UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Note to Reader
September 9, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

June 3, 1998

MEMORANDUM

SUBJECT: The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Tribuphos. PC Code 074801; List B, Case No. 2145
DP Barcode 222993

FROM: Robert Travaglini, Chemist
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THROUGH: Steven Knizner, Branch Senior Scientist
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

TO: Thomas Luminello, Special Review Manager
Special Review Branch
Special Review and Reregistration Division (7508W)

Please find attached the Human Health Assessment for the Tribuphos Reregistration Eligibility Decision Document (RED) Case No. 2145. This Chapter compiles the completed disciplinary chapters from: Toxicology by Robert Zendzian, the Product and Residue Chemistry by Catherine Eiden, Occupational/Residential Exposure Assessment by Brenda Tarplee, and the Dietary Risk Analysis (DRES) by Brian Steinwand.

Required Data:

Chemistry

Magnitude of the Residues - Crop Field Trials (§ 171-4; d, j)

Toxicology

Acute Neurotoxicity - rat (§ 81-8)

Subchronic Neurotoxicity - rat (§ 82-5)

Special Subchronic Neurotoxicity - rat (non-guideline study)

Please note that HED has not yet reviewed a recently submitted residue chemistry study: 171-4; k (cottonseed and gin byproducts), prior to issuing this RED chapter. Therefore some of the dietary exposure assessments (concerning milk, meat and meat by-products) may need to be revised based upon the results of the review of the submitted study. However, HED's concerns over occupational exposure and risk estimates will remain. The occupational assessment was based on PHED data and using chemical specific post-application exposure studies. Meetings/discussions should be initiated to discuss occupational mitigating options such as labeling for this chemical.

cc.: R. Travaglini, RCAB/HED (7509C)
S. Knizner, RCAB/HED (7509C)
RCAB Files (7509C)
DRES Files (7509C)
R. Zendzian, SAB/HED (7509C)
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THE HED TRIBUPHOS SCIENCE CHAPTER

I. EXECUTIVE SUMMARY

The Health Effects Division (HED) has evaluated the tribuphos data base and determined that the data are adequate to support reregistration. The toxicological data base is adequate to support reregistration, although some data gaps exist. Residue chemistry requirements are substantially complete pending residue field trial data for cotton gin byproducts.

Tribuphos, also known as DEF, is an organophosphate defoliant/desiccant used on cotton crops. It is primarily used to defoliate cotton in preparation for machine harvesting. It is also used as a defoliant to reduce or prevent losses from boll rot organisms and in conjunction with ultimate insecticide application to accelerate the aging of cotton leaves. Tribuphos is manufactured and sold in the United States by Bayer Corporation (formerly Miles-Mobay Corporation, Inc.).

Hazard Assessment

The toxicology data base provides overwhelming evidence confirming that tribuphos like other organophosphates has anticholinesterase activity in all species tested including dogs, rabbits, rats, mice and hens. By the oral and dermal routes technical tribuphos is classified in Toxicity Category II and by the inhalation route, Category IV. No data are available on eye irritation. Dermal irritation is mild to moderate, Toxicity Category IV. Tribuphos is not a dermal sensitizer. Inhibition of plasma, erythrocyte and brain cholinesterase (ChE) activity occurs by all routes of exposure (oral, dermal and inhalation), and following exposure for various durations. The Lowest Observed Effect Levels (LOELs) for ChE inhibition occurred at the 0.4 mg/kg/day dosing level (oral) in a dog chronic toxicity study.

In addition to its neurotoxicity secondary to cholinesterase inhibition, tribuphos displayed organophosphate type delayed neurotoxicity in the hen. Tribuphos also displayed toxicity of the visual system in the rat (following either oral or inhalation exposure). The irreversible visual system toxicity is manifested histopathologically by bilateral retinal atrophy (obliteration) at 12 months and atrophy of the optic nerves at 24 months in a lifetime feeding study in the rat. Based on these finding, a special 90 day neurotoxicity study in the rat is required. The retinal effects were seen at dosing levels of approximately 15 mg/kg/day (oral or inhalation exposures converted to oral equivalents.

The Cancer Peer Review Committee met to evaluate the cancer classification of tribuphos. Using the revised Cancer Guidelines, the committee concluded that based on the overall evidence in animals, tribuphos should be characterized as a “likely" carcinogen at high doses, based on increases in tumors in both sexes of CD-1 mouse and “unlikely" at low doses since all the tumor increases occurred only at the highest dose tested (35.7 mg/kg/day), accompanied by severe toxicity. A linear assessment based on tumors was not recommended, because of severe accompanying toxicity, typical of organophosphate chemicals, which occurred at all doses in the mouse. Therefore a non-linear approach (MOE) utilizing the most sensitive toxic endpoint for

chronic toxicity was recommended. The most sensitive endpoint for chronic toxicity was plasma cholinesterase inhibition (NOEL of 0.1 mg/kg/day established in the dog chronic toxicity study).

The metabolism of tribuphos in rats indicates that >90% of the administered dose was excreted in 72 hours and there was no significant tissue residue. Absorbed material was extensively and completely metabolized.

Thorough review of the available database reveals that tribuphos is not a developmental, reproductive or mutagenic toxicant.

The Hazard Identification Assessment Review Committee (HIARC) recommended that the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. Although no increased sensitivity of fetuses as compared to maternal animals were observed following *in utero* exposure in developmental toxicity studies and no increased sensitivity of pups as compared to adults were observed in a multi-generation reproduction study, the Committee determined that the 10x factor is required because: (1) data gaps for acute and subchronic neurotoxicity studies; (2) evidence of neuropathological lesions; and, (3) concern for the developmental neurotoxic potential of tribuphos, based on the evidence of neuropathological lesions in the subchronic study with hens and in the combined chronic toxicity/carcinogenicity study in rats. The OPP FQPA Safety Factor Committee will make a final determination as to the applicability of the FQPA factor. For risk estimates presented in this assessment, the 10x was applied as per the HIRAC recommendation.

Six exposure and risk assessments were conducted for tribuphos: acute dietary, chronic dietary (non-cancer), chronic dietary (cancer), non-dietary short- and intermediate-term dermal, and non-dietary inhalation (for any time period). The acute and chronic dietary assessments capture exposure estimates for the general public. The latter three assessments are for occupational exposures. The six different assessments were conducted separately based on different hazard (toxicological) endpoints.

For the acute dietary risk assessment, the toxic endpoint selected was the NOEL of 1 mg/kg/day, based on cholinesterase inhibition (plasma and RBC) at the LOEL of 7 mg/kg/day in the rat developmental toxicity study. A MOE 1000, based on interspecies extrapolation (10x), intraspecies variability (10x), and the FQPA 10x factor, is considered adequately protective.

For the chronic dietary (non-cancer) and exposure risk assessment, the RfD was established based on the dog chronic toxicity study. The NOEL of 0.1 mg/kg/day was based on plasma cholinesterase inhibition at the LOEL of 0.4 mg/kg/day. The RfD is 0.0001 mg/kg/day based on interspecies extrapolation (10x), intraspecies variability (10x), and the FQPA 10x factor.

For Short- and Intermediate-term dermal risk assessments, the LOEL of 2 mg/kg/day (the lowest dose tested, a NOEL was not established) was selected as the endpoint for risk assessment. The

LOEL was based on dose-dependent inhibitions of plasma, RBC and brain cholinesterase activity from a 21-day dermal toxicity study in rabbits. This endpoint was supported by the LOEL of 2.6 mg/kg/day in the 90-day dermal toxicity study in hens. A NOEL for whole blood cholinesterase was also not established in the hen study. HIRAC recommended the application of uncertainty factors (UF) to account for inter-species (10x) and intra-species (10x) extrapolation, with an additional UF of 10x for the use of a LOEL and due to the observance of severe neurotoxic effects seen in the hen study. Note that the additional UF of 10 is applied based on FIFRA considerations and not for FQPA. As per current OPP policy, the FQPA factor is not applicable for occupational exposure risk assessment.

For short- and intermediate-term inhalation risk assessments the NOEL of 2.43 mg/L (0.9 mg/kg/day) established in the 90-day inhalation study in rats was used. The LOEL of 12.2 mg/L (4.5 mg/kg/day) was based on RBC and plasma cholinesterase inhibition. A MOE of 100 is adequate because a NOEL is used for this risk assessment.

Exposure Assessment

Dietary (Food) Exposure

Dietary exposure to tribuphos can occur via residues present in cottonseed oil or as a result of transfer of residues from livestock feed items (cotton gin-byproducts, cottonseed hulls and cottonseed meal) to meat and milk. Since residue field trial data for cotton gin by-products are not available, an estimate of residues on this livestock feedstuff was made extrapolating data from the cotton metabolism study. HED recognizes that the resulting maximum theoretical dietary burden may be conservative; however, because of the lack of data for cotton-gin byproducts, further refinements to dietary burden calculations cannot be made at this time. Crop field trial data for cotton gin by-products will be required as a condition of reregistration.

The existing tolerances for meat, meat byproducts (mbyp), and fat are all 0.02 ppm; the existing milk tolerance is 0.002 ppm. Based on the maximum theoretical dietary burden for livestock, the existing tolerance is adequate to cover residues of tribuphos expected in meat and mbyp. However, the existing tolerance for fat should be increased to 0.15 ppm and the tolerance for milk should be raised to 0.01 ppm.

The acute dietary exposure analysis estimates the distribution of single-day exposure for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of tribuphos in the commodity supply. The acute dietary exposure analysis is considered an overestimate of exposure since it assumes tolerance level residues for all commodities having tribuphos tolerances and 100% of crop is treated. Additionally, because of data gaps, conservative assumptions were used to reassess tribuphos tolerances for meat/milk.

A partially refined chronic dietary exposure assessment was conducted. Tolerance level residues were assumed for all commodities having tribuphos tolerances. As previously noted, conservative assumptions were used to estimate exposure to tribuphos residues from meat/milk. Percent-crop treated data were used for cottonseed oil and meal .

Dietary (Water) Exposure

Estimated environmental concentrations (EECs) from surface water sources was provided by EFED. Because environmental fate testing indicates that tribuphos binds to the soil and appears to be immobile, EFED was not concerned about residues of tribuphos in ground water. Based on the results of a Tier 2 analysis (PRIZM/EXAM II), tribuphos residues can potentially be present in surface waters. The estimated environmental concentrations (EECs) were 14 ppb for day 0 (maximum concentration) and the average EEC was 5 ppb.

Occupational Exposure

Occupational exposure data obtained from the Pesticide Handlers Exposure Data Base, (PHED) Version 1.1, were used to calculate short-term and intermediate-term dermal and inhalation exposure to tribuphos. Tribuphos chemical specific occupational exposure data have been submitted to the Agency and are a component of the PHED Version 1.1 database. Based on the tribuphos use patterns, HED has identified five scenarios for short-term and intermediate-term occupational dermal and inhalation exposure to tribuphos residues: pesticide handlers, mixers, loaders, applicators and flaggers. Long-term occupational exposures are not expected to occur for the registered uses of tribuphos. The PHED data used to estimate occupational exposure are all rated “Best Available”, high or medium confidence. “Best Available” is defined by HED as meeting OPP Subdivision U Guidelines.

HED identified four exposure scenarios for post-application exposure to tribuphos: picker operator, module builder operator, raker and tramper. A chemical specific study was used to determine dermal and inhalation exposures for these scenarios. Worker exposures were calculated using dosimetry data obtained from this study. Exposure estimates for post-application activities are therefore highly refined.

Risk Characterization

Dietary Risk (Food):

Acute

The risk estimate for acute dietary exposure exceeds HED's levels of concern. Reassessed tolerance level residues on commodities result in margins of exposure (MOEs, at the 95th percentile) of 700 for children (1-6 years old) and 625 for infants (<1 year). The acute dietary risk estimate expressed as a MOE for the general U.S. population is 1250. As previously noted, this analysis is conservative in that it assumes tolerance level residues and 100% crop-treated for all commodities with tribuphos tolerances. This risk estimate is most likely driven by exposure to residues from meat and milk products. As noted previously, the reassessed tolerance for milk is based on conservative assumptions because of the lack of residue field trial data for cotton gin byproducts.

Chronic (Non-Cancer)

The risk estimate for chronic (non-cancer) dietary exposure from the registered uses of tribuphos, exceeds HED's level of concern for the US Population and all DRES subgroups, including infants and children. Reassessed tolerance level residues on commodities result in exposures which are 254% of the RfD for the US population and 750% of the RfD for non-nursing infants < 1 year old. Because residue field trial data for cotton gin by-products were not available, some conservative assumptions were made to calculate potential residues in meat and milk. Dairy products contribute 652% of the RfD for non-nursing infants.

Chronic (Cancer)

Using the same partially refined chronic dietary exposure assumptions, the cancer MOE for the U.S. population is calculated to be 1100 when using reassessed tolerances. As per the recommendation of the CPRC, a non-linear approach (MOE) utilizing the most sensitive toxic endpoint for chronic toxicity was used. The most sensitive endpoint for chronic toxicity was plasma cholinesterase inhibition (NOEL of 0.1 mg/kg/day established in the dog chronic toxicity study). Using the revised Cancer Guidelines, the CPRC concluded that based on the overall evidence in animals, tribuphos should be characterized as an "unlikely" carcinogen at low doses, and a "likely" carcinogen at high doses. We note that all the tumor increases in mice occurred only at the highest dose tested (35.7 mg/kg/day), accompanied by severe toxicity.

Dietary Risk (Drinking Water)

Because the acute and chronic exposure to infants and children from food alone exceeds HED's levels of concern, no exposure to tribuphos in drinking water is acceptable. Since tribuphos is may be found in surface waters, aggregate dietary risk would include exposure to tribuphos through drinking water.

Currently, HED uses DWLOCs as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses (if any). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

Non-Occupational (Residential) Risk:

There are no registered residential uses of tribuphos. HED does not expect any residential exposure scenarios to exist for registered uses of tribuphos. Therefore, no exposure or risk calculations for residential uses are warranted.

Occupational Risk:

Application Exposure - **Handler/Mixer/Loader/Applicator/Flagger scenarios exceed HEDs level of concern for dermal risk. Risk estimates, expressed as MOEs for dermal exposure are less than 1000 despite maximum mitigation measures for the 5 identified exposure scenarios**: (1a) mixing/loading for aerial application; (1b) mixing/loading liquids for groundboom application; (2) applying sprays with fixed-wing aircraft; (3) applying sprays with a helicopter; (4) applying sprays with a groundboom sprayer and (5) flagging liquid aerial applications (1,200 acres treated).

Post-Application Exposure - **HED has concern for reentry workers exposure to tribuphos**. In all 4 exposure scenarios, risk estimates indicated that MOEs are less than 1,000 only after a minimum post-application reentry interval of 20 days. Post application calculations of risk for re-entry into tribuphos-treated cotton fields result in MOEs above 1000 only after the following number of days after treatment:

Picker Operator - 26 days after treatment
Module Builder Operator - 20 days after treatment
Raker - 28 days after treatment
Tramper - 30 days after treatment

Mitigation measures and labeling requirements to address these concerns have been deferred pending a meeting/decision with SRRD on handler and post-application risk mitigation. Additional handler and post-application studies may be required pending the outcome of these discussions.

Aggregate Risk

The aggregate acute and chronic dietary risk includes exposures to tribuphos residues in food and water. However, HED notes that exposure to tribuphos residues in food alone exceed HED's

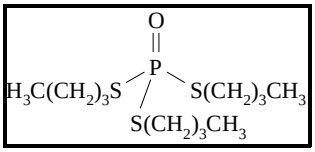
levels of concern for both acute and chronic dietary risk. At this point in time and until the exposure to tribuphos in the diet is reduced or a more refined acceptable risk assessment is provided, any additional exposure to tribuphos through drinking water would only cause acute and chronic risk estimates to further exceed HED's level of concern. In effect, the drinking water level of concern (DWLOC) for acute and chronic effects of tribuphos is zero. Tier 2 modeling for surface water indicates that tribuphos may be found in surface water. Tribuphos is not expected to be found in groundwater.

Aggregate Risks for Short and Intermediate Term exposure were not estimated since there are no residential exposures expected with registered uses.

II. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

Tribuphos (also named tribufos, DEF and DEF6) [*S,S,S*-tributyl phosphorotrithioate] is an emulsified concentrate (EC) cotton defoliant registered for use as a total defoliant and as a bottom defoliant to reduce or prevent losses from boll rot organisms, and also as a mix with the last insecticide application to accelerate the aging of cotton leaves.



Empirical Formula: $C_{12}H_{27}OPS_3$
Molecular Weight: 314.5
CAS Registry No.: 78-48-8
Shaughnessy No.: 074801

Tribuphos is a colorless to yellow liquid with a mercaptan-like odor and a boiling point of ~150 C. Tribuphos is practically insoluble in water (2.3×10^{-4} g/100 ml), but is completely miscible in dichloromethane, n-hexane, 2-propanol, and toluene. Tribuphos is relatively stable to heat and under acidic conditions, but slowly hydrolyzes under alkaline conditions.

A search of the Reference Files System (REFS) conducted 1/24/96 identified a single manufacturing-use product (MP) registered to Bayer Corporation (formerly Mobay Corporation then Miles, Inc.) under Shaughnessy No. 074801, the 92% technical (T; EPA Reg. No. 3125-96). Only the Bayer tribuphos T/TGAI (Technical Grade Active Ingredient) is subject to a reregistration eligibility decision.

Table 1: PRODUCT CHEMISTRY DATA SUMMARY ON THE TECHNICAL

Guideline Number	Requirement	Are Data Requirements Fulfilled? [a]	MRID Number [b]
61-1	Product Identity and Disclosure of Ingredients	Y	41618801
61-2	Starting Materials and Manufacturing Process	Y	41618801
61-3	Discussion of Formation of Impurities	Y	41618801
62-1	Preliminary Analysis	Y	41618802
62-2	Certification of Ingredient Limits	Y	41618802
62-3	Analytical Methods to Verify the Certified Limits	Y	41618802

Table 1: PRODUCT CHEMISTRY DATA SUMMARY ON THE TECHNICAL

Guideline Number	Requirement	Are Data Requirements Fulfilled? [a]	MRID Number [b]
63-2	Color	Y	41618803
63-3	Physical State	Y	41618803, **42382701**
63-4	Odor	Y	41618803
63-5	Melting Point	N/A [c]	
63-6	Boiling Point	Y	41618803
63-7	Density, Bulk Density or Specific Gravity	Y	41618803
63-8	Solubility	Y	41618803
63-9	Vapor Pressure	Y	41618803
63-10	Dissociation Constant	N/A [d]	
63-11	Octanol/Water Partition Coefficient	Y	41618803
63-12	pH	Y	**42382701**
63-13	Stability	Y	41618803

[a] Y = Yes; N = No; N/A = Not Applicable.

[b] All citations were reviewed under CBRS No. 8291, D166323, 12/9/91, K. Dockter, except for those **bolded** citations which were reviewed under CBRS No. 10286, D180879, 9/8/92, F. Toghrol.

[c] Data are not required because the TGAI is a liquid at room temperature.

[d] Data are not required because the TGAI/PAI does not dissociate.

All of the pertinent data concerning the tribuphos TGAI are satisfied for the purposes of reregistration.

B. Human Risk Assessment

1. Hazard Assessment

a. Acute Toxicity

Table 2: Acute Toxicity of Tribuphos

Guideline No.	Study Type	Results	Toxicity Category	MRID #s
81-1	Acute Oral	LD_{50} =192-235 mg/kg	II	41954903
81-2	Acute Dermal	LD_{50} =>1000 mg/kg (m) <2000 mg/kg (f)	II	41954902
81-3	Acute Inhalation	LC_{50} =4650 mg/m^3 (m) 2460 mg/m^3 (f)	III	41782301
81-4	Primary Eye Irritation	data required (irritation likely)	na	none
81-5	Primary Skin Irritation	mild to moderate erythema, dry cracked skin, edema	IV	41896203
81-6	Dermal Sensitization	negative	-	41618812
81-7	Acute Neurotoxicity hen	data not required*	-	none

Sufficient data are available on the acute inhalation toxicity of tribuphos in the rat. Doses tested in a four hour nose only exposure were; males 2920, 5690 or 6030 mg/kg (equivalent to 1081, 2107 or 2233 mg/kg, respectively); females 1590, 2920 or 3190 mg/m^3 (equivalent to 589, 1081 or 1181, respectively). Signs indicative of cholinesterase inhibition were observed at all doses. The LC_{50} for males was 4650 (1410-6180) mg/m^3 and for females 2460 mg/m^3. Toxicity Category III. MRID 41782301

Sufficient data are available on the primary dermal sensitization properties of tribuphos in the guinea pig. Tribuphos was not a sensitizer when tested with the Buehler Topical Closed-Patch test. MRID 41618812.

(* Literature references and an acceptable 90-day dermal study in the hen show that tribuphos produces organophosphate type delayed neurotoxicity. Therefore, an acute study is not required in the hen.)

b. Subchronic Toxicity

Sufficient data are available on the subchronic (21-day) dermal toxicity of tribuphos in the rabbit. Doses tested, 0, 2, 10 or 25 mg/kg/day nominal (0, 2, 11 or 29 mg/kg/day actual). At 29 mg/kg/day I male and 4 females died or were sacrificed in extremis. Signs of dose-related toxicity were observed in both sexes at 11 and 29 mg/kg/day, with a greater effect at the higher dose. Mild to moderate dermal irritation was observed at 11 and 29 mg/kg/day in both sexes. At termination, dose-related depression of cholinesterase activity was observed in all doses in both sexes in plasma, erythrocyte (RBC) and brain. Statistically significant depression ($p<0.05$) was observed in plasma (males) and erythrocytes (females) at 2 mg/kg/day and in all parameters in both sexes at 11 and 29 mg/kg/day. No recovery was observed in erythrocyte and brain cholinesterase activity at 33-34 days (14 days post dose). MRID 42007201

Sufficient data are available on the subchronic (90-day) inhalation toxicity of tribuphos in the rat. Doses administered were 0, 0.93, 2.43, 12.2 or 59.5 mg/m^3 actual (0, 0.3, 0.9, 4.5, 22 mg/kg/day). Cholinesterase inhibition in the RBC at 12 and 60 mg/m^3 in both sexes, in the plasma at 12 and 60 mg/m^3 in males, at 60 mg/m^3 in females, and in the brain at 60 mg/m^3 both sexes. The adrenals showed cortical fat deposition at 60 mg/m^3 in both sexes. The ERG (Electro Retiniogram) was depressed (a- and b- waves) at 60 mg/m^3 in both sexes indicative of a toxic effect on the rods and cones of the retina (MRID 42399801). We note that retinal toxicity was also observed in the rat chronic/oncogenicity, the high dose in each of these studies produced essentially the same exposure (17 mg/kg/day) and as such, the effect on the ERG in the inhalation study can be considered predictive of the retinal damage observed in the chronic/oncogenicity study (see below).

No data are available in the subchronic oral toxicity of tribuphos. Studies are not required in the rodent and non-rodent species because acceptable chronic studies are available in the rat and dog.

c. Chronic Toxicity and Carcinogenicity

In the oral chronic toxicity study (MRID 42335101) in the rat, complete bilateral retinal atrophy (obliteration) was observed at 12 months at the high dose, 16.8 mg/kg (320 ppm). At 24 months statistically significant ocular damage at the high dose included cataract, lens opacity, corneal opacity, corneal neovascularization and bilateral retinal atrophy (obliteration). At doses of 0, 0.2 and 1.8 mg/kg/day ppm terminal retinal atrophy was generally unilateral and histopathologically different from that seen at the high dose.

In a combined chronic toxicity/oncogenicity study in the Fisher 344 rat doses

were 0, 4, 40 or 320 ppm (equivalent to 0.0, 0.2, 1.8 and 16.8 mg/kg/day in males; and 0.0 0.2, 2.3 and 21.1 mg/kg/day in females). No oncogenic response was observed. However, a variety of nononcogenic compound related effects were observed: 0.2 mg/kg/day decreased plasma cholinesterase was observed in both sexes. At 1.8 mg/kg/day decreased weight gain, cholesterol and calcium were observed in males; and decreased RBC cholinesterase, RBC count, hemoglobin, and hematocrit were observed in both sexes. At 16.8 mg/kg/day decreased weight gain in the females was observed. At 16.8 mg/kg/day the following was observed In males and females:

- increased food consumption,
- terminal opthamological exam; cataract, lens opacity, corneal opacity, corneal neovascularization, iritis/uveitis,
- terminal ERG; unrecordable,
- decreased total protein, globulin, cholesterol, calcium,
- increased BUN,
- decreased brain cholinesterase,
- adrenals; vacuolar degeneration (12mos),
- eyes; retinal atrophy (12mos),
- small intestine; autolysis, vacuolar degeneration (12mos),
- eyes; retinal atrophy, uveitis, cataract, neovascularization (24mos),
- optic nerves; atrophy (24mos),
- small intestine; autolysis, vacuolar degeneration, hyperplasia (24mos)

The LOEL in both sexes for plasma cholinesterase is 0.2 mg/kg/day, the Lowest Dose Tested (LDT). The LOEL for RBC cholinesterase inhibition in both sexes is 1.8 mg/kg/day and the NOEL is 0.2 mg/kg/day. The LOEL for brain cholinesterase inhibition in both sexes is 16.8 mg/kg/day and the NOEL is 1.8 mg/kg/day. (MRID 42553601)

In the mouse oncogenicity study, mice CD-1 were dosed at 0, 10, 50 or 250 ppm (equivalent to 0, 1.4, 7, and 35.7 mg/kg/day) for 90 weeks. At 10 ppm, decreased plasma and RBC cholinesterase was observed in both sexes and decreased brain cholinesterase in males. At 78 weeks males showed decreased MCV (Mean Corpuscular Volume) and MCH and at week 90 females showed decreased hematocrit. At 50 ppm, an increased number of males showed paleness and hunched backs. At 78 weeks males showed decreased MCV and MCH and at week 90 decreased MCH. At week 90 females showed decreased RBC count, hemoglobin and hematocrit. Histopathology of the males showed; adrenals amyloid, epididymis hyperspermatogenensis, small intestine amyloid and vacuolar degeneration epithelium, spleen hematopoiesis. At 250 ppm loose stools were observed in females, enlarged abdomen in both sexes, increased mortality/decreased life span in both sexes and increased food consumption and body weight in both sexes. Decreased RBC count,

hemoglobin, hematocrit, MCV and MCH was observed in males and decreased RBC count, hemoglobin and hematocrit in females. Histopathology in males showed; adrenals degeneration, liver hemangiosarcoma, rectum acute inflammation, necrosis aid ulcer, small intestine adenocarcinoma, dilated/ distended and mucosal hyperplasia. In females histopathology showed; adrenals calcification and degeneration/ pigmentation, caecum edema, liver hypertrophy, lung alveolar/ bronchiolar adenoma*, mesenteric lymph node congestion, rectum acute inflammation, necrosis and ulcer, small intestine adenocarcinoma* dilated/distended, mucosal hyperplasia. (*statistically significant increase in tumors). The LOEL for plasma cholinesterase inhibition is 10 ppm (LDT, males and females). The LOEL for brain cholinesterase inhibition is 10 ppm in males and 50 ppm in females, the NOEL for females is 10 ppm. The systemic LOEL (both sexes) is 50 ppm based on cholinesterase inhibition and the LOEL is 10 ppm. (MRID 41171001).

A chronic study was performed in the Beagle dog at doses of 0, 4, 16 or 64 ppm (equivalent to 0, 0.1, 0.4, or 1.7 mg/mg/day in males; 0, 0.1, 0.4, or 2.0 mg/kg/day in females). Inhibition of plasma cholinesterase was observed in both sexes at the mid dose level. Inhibition of erythrocyte cholinesterase was observed in both sexes at the high dose. A possible decrease in the number of erythrocytes at 64 ppm was observed in both sexes (1.7 mg/kg males, 2.0 mg/kg females). No other toxic effects were observed. The LOEL for plasma cholinesterase is 16 ppm (0.4 mg/kg) and the NOEL is 4 ppm (0.1 mg/kg). The LOEL for erythrocyte cholinesterase is 64 ppm (1.7 mg/kg) and the NOEL is 16 ppm. The NOEL for brain cholinesterase inhibition is 64 ppm (HDT). (MRID 42007203)

d. Developmental Toxicity

In the rat teratology study, pregnant Charles River Crl:CD® rats were gavaged at dose levels 0, 1, 7 or 28 mg/kg/day (gestations days 6-16). Maternal RBC and plasma cholinesterase activity was depressed at 7 and 28 mg/kg/day, and brain activity at 28 mg/kg/day. No teratogenic effects were observed. Maternal weight gain was decreased at 28 mg/kg/day. The maternal toxicity LOEL is 7 mg/kg/day based on plasma and RBC cholinesterase inhibition and the NOEL is 1 mg/kg/day. The developmental NOEL is 28 mg/kg/day (HDT). (MRID 4019O601)

In the American Dutch rabbit teratology study, pregnant rabbits were gavaged at dose levels of 0, 1, 3 or 9 mg/kg/day, (gestation days 7-19). Plasma and RBC cholinesterase activity were significantly reduced at all doses on day 20 and RBC at all doses on day 28. Does failed to gain weight at 9 mg/kg/day during dosing. The maternal toxicity LOEL is 1 mg/kg/day (LDT) based on plasma and erythrocyte cholinesterase inhibition. The systemic LOEL is 9 mg/kg/day based on decreased mean weight gain and the NOEL is 3 mg/kg/day. The developmental NOEL is 9

mg/kg/day (HDT). Tribuphos was not teratogenic in this study. (MRID 40190602)

e. Reproductive Toxicity

In a 2-generation reproduction study, Sprague-Dawley rats were dosed at 0, 4, 32 or 260 ppm (equivalent to 0, 0.2, 1.7 or 15 mg/kg/day). The only compound-related effect on reproduction was a significant increase in dead pups in the Fla and F2a litters (LOEL 260 ppm, NOEL 32 ppm). The most sensitive effect was blood cholinesterase inhibition in adults. In pups, decreased cholinesterase activity was greatest at 21 days in the Fla females and plasma cholinesterase activity significantly decreased. The adult LOEL for plasma and erythrocyte cholinesterase inhibition is 0.2 mg/kg/day (LDT). The pup LOEL for plasma and erythrocyte cholinesterase inhibition is 15 mg/kg/day and the NOEL is 1.7 mg/kg/day. The reproductive LOEL is 15 mg/kg/day and the NOEL is 1.7 mg/kg/day. The systemic LOEL is 1.7 mg/kg/day based on decreased body weight gain and the NOEL is 0.2 mg/kg/day. (MRID 42040101)

A cross fostering study to determine if pup loss in the 2 -generation reproduction study (MRID 42040101) was due to treatment of dams, pups in utero or both. Male and female Sprague-Dawley rats, were assigned to each of four test groups of 15 males and 30 females each. (Group 1: treated with pups with untreated dams; Group 2: untreated dams and pups; Group 3: untreated pups, treated dams; Group 4: treated pups and dams.) Groups 1 and 2 received 0 ppm and groups 3 and 4 received 260 ppm (15 mg/kg/day) tribuphos in the diet. After 10 weeks on the test diet these animals were bred within their test groups. After birth, pups from groups 1 and 3 were cross fostered so that the 0 ppm dams reared pups from 260 ppm fed dams and the 260 ppm dams reared from 0 ppm dams. Pups from group 2 and 4 were cross fostered within the test groups. That is, pups from 0 ppm dams were raised by 0 ppm dams that were not their birth dams and the same with pups from 260 ppm dams. Mean pup loss was 0.00, 0.47, 1.50 or 2.85 per litter for groups 1-4, respectively. Cannibalism was observed in treated dam groups (3 and 4). Evidence for both mechanisms plus a synergistic effect was observed in group 4. (MRID 42040103)

f. Mutagenicity

Sufficient data are available on the mutagenic potential of tribuphos. Tribuphos was negative in all tests.

A mutagenicity study was performed in salmonella. Tester systems used were the Salmonella typhimurium histidine auxotrops TA98, TA1000, TA1537 and TA1538 as described by Ames et al (1975). The test compound was negative without and with microsomal activation at concentrations up to 10,000 µg/plate. (MRID 41459101)

A study of unscheduled DNA synthesis was preformed on rat primary hepatocytes. The test compound was negative at concentrations of 0.0001 to 0.006 µg/ml. Higher concentrations were cytotoxic. (MRID 41459102)

A test for chromosomal aberrations was performed in Chinese hamster ovary cells. The test compound was negative without and with microsomal activation. Doses tested without activation, 0.004, 0.007, 0.013, 0.025 and 0.05 ul/ml, showed toxicity at 0.025 and 0.05 ul/ml. Doses tested with activation, 0.007, 0.013, 0.025, 0.05 and 0.1 ul/ml, showed toxicity at 0.05 and 0.1 ul/ml. (MRID 41459103)

g. Metabolism

Sufficient data are available on the metabolism of tribuphos in the rat.

In the metabolism study of [1- C^{14}] Tribuphos was performed in 5 male and 5 female rats single oral dose, 5mg/kg or 100 mg/kg or 5 mg/kg/day X 14 days cold tribuphos followed by 5 mg/kg [1-C^{14}] Tribuphos. 55 to 80 % was absorbed of which 90+% was excreted in 72 hours. There was no significant tissue residue. Absorbed material was extensively and completely metabolized. (MRID 42034501)

h. Neurotoxicity

Sufficient data are available on the subchronic neurotoxicity of tribuphos by the dermal route in hens to detect Organophosphate induced delayed nueropathology (OPIDN). A 90-day dermal neurotoxicity study (MRID 42007202) was performed in hens. Doses tested were O, 2.6, 11 or 42 mg/kg/day. Triothrocresolphosphate (TOCP) was utilized as a positive control at 18 mg/kg/day. Doses were applied to the comb of the hen. Effects observed in the tribuphos treated hens were failure to gain weight, ataxia in seven of twelve hens (LOEL 42 mg/kg/day, NOEL 11 mg/kg/day) and whole blood cholinesterase inhibition. Histopathology indicative of neurotoxicity was observed primarily in the brain and spinal cord. The LOEL for whole blood cholinesterase inhibition is 2.6 mg/kg/day (LDT). The systemic LOEL is 11 mg/kg/day based on decreased weight gain and the NOEL is 2.6 mg/kg/day. The neurotoxic LOEL is 42 mg/kg/day based on the histopathology of the brain and spinal cord and the NOEL is 11 mg/kg/day. (MRID 42007202)

In addition to its neurotoxicity secondary to irreversible cholinesterase inhibition, tribuphos displayed organophosphate type delayed neurotoxicity in the hen and toxicity of the visual system in the rat. The visual system toxicity is manifested histopathologically by bilateral retinal atrophy (obliteration) at 12 months and atrophy of the optic nerves at 24 months in a lifetime feeding study in the rat. These effects were also observed in the rat subchronic inhalation study

Effect and no effect levels for cholinesterase inhibition have been demonstrated in the rat, rabbit and dog by the full battery of toxicity tests (oral, dermal and inhalation) which monitor this parameter.

Effect and no effect levels for organophosphate type delayed neurotoxicity have been demonstrated by clinical observation and by histopathology in a 90-day dermal study in the hen. Histopathological examination of the nervous system followed in situ perfusion and fixation. This method minimizes artifacts induced by removal of the tissue and allows for highly sensitive detection of chemical induced lesions. Also, the hen is sensitive to this unique human toxicity and the rodent (rat or mouse) is not.

Effect and no effect levels for the visual system toxicity have been demonstrated in the rat lifetime feeding study. However, the unique toxicity [bilateral retinal atrophy (obliteration) at the high dose at 12 months] is manifest as a completed process at the first scheduled sacrifice. The retina and its unique cells are gone. Sometime during the 12 month dosing period the cells of the retina were killed by the treatment and removed. It is necessary, for risk assessment, to determine when this irreversible process started. The subsequent optic nerve atrophy also indicated the possibility of additional CNS toxicity. Although the brain and spinal cord were examined histopathologically in the lifetime study at 12 and 24 months they were not perfused in situ. All of this indicated the necessity for a special 90-day feeding neurotoxicity study in the rat.

The special 90-day neurotoxicity study in the rat must include cholinesterase determinations (before, during and at termination), electroretinograms [ERG] (before, during and at termination) and histopathology of the nervous system after in situ fixation. Tissues examined must include the eye, brain, spinal cord and representative peripheral nerves. The functional observation battery is not necessary. The high dose must be at least as high as that in the chronic rat feeding study (16.8 mg/kg/day). A higher dose may be considered in order to hasten the onset of neurotoxicity. A study protocol should be submitted to HED before commencing the study.

i. Dermal Absorption

Sufficient data are available on the dermal absorption of tribuphos.

A dermal absorption study was (MRID 42350003) performed in the rat at doses of 2.8, 14.0 or 140 ug/cm^2 and exposures of 1, 4 and 10 hours plus a 10 hour wash with 168 hr exposure. (158 hours after exposure, the animals were sacrificed.) Significant skin residue remained after the soap and water wash at 1, 4, and 10 hours (30-40%). the 10 hour residue was mostly absorbed at 168 hrs. Maximum absorption was 34-44 % after the 168 hour exposure.

2. Dose Response Assessment

On January 23, 1997, the HED's RfD/Peer Review Committee evaluated the toxicology data base of tribuphos and reassessed the reference dose (RfD) and concluded that the use of an additional uncertainty factor (UF) for enhanced sensitivity for infants and children (as required by FQPA) was not warranted. This decision was based on the lack of evidence of increased sensitivity in the developmental studies in rats and rabbits and the two-generation reproduction study in rats (Memo: G. Ghali, HED to P. Errico, RD, dated 07/14/97).

On January 28, 1997 the HED's Toxicology Endpoint Selection Committee (TESC) selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments but did not address the Margins of Exposure (MOEs) required for the various exposure scenarios (Document dated 3/6/97).

On November 25, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the UFs and MOEs for dietary as well as non-dietary risk assessments in the RfD Committee and TESC meetings. This re-evaluation was necessitated to ensure consistency with the other organophosphate chemicals that were recently reviewed by the HIARC to address the enhanced sensitivity of infants and children as required by the FQPA. HIARC's decisions are summarized below.

a. Sensitivity to Infants and Children

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children." The following data were reviewed in order make a determination to retain, reduce or remove this 10 fold FQPA factor.

Weight of the Evidence

Neurotoxicity

- # Acute and subchronic neurotoxicity studies in rats are a data gap. Thus, data on cholinesterase inhibition, Functional Observation Battery, as well as histopathology of the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to Tribuphos.

- # In the subchronic dermal delayed neurotoxicity study (MRID 42350003) in hens, a NOEL was not established and the LOEL was 2.6 mg/kg/day (LDT) based on the whole blood cholinesterase inhibition.

Developmental Toxicity

- # The developmental toxicity studies in rats (MRID 40190601) and rabbits (MRID 40190602) showed no evidence of additional sensitivity of young rats or rabbits following pre- or postnatal exposure to tribuphos.

Reproductive Toxicity

- # In a two-generation reproduction study (MRID 42040101) there was no increased sensitivity of pups over the adults. The parental systemic LOEL was 4 ppm (0.2 mg/kg/day) based on inhibition of plasma cholinesterase activity; a parental systemic NOEL was not established. For reproductive toxicity, the NOEL was 32 ppm (1.7 mg/kg/day) and the LOEL was 260 ppm (15 mg/kg/day) based on: 1) significant increases in the number of litters with stillborn pups and pup death (including cannibalism) throughout lactation; 2) decreases in F_1 and F_2 pup body weights, and; 3) significant increase in the F_1 gestation period.

Cholinesterase Inhibition

- # In the developmental toxicity studies, cholinesterase activity was measured in adults but not in the pups, thus a comparisons could not be made on the effect of tribuphos in this biomarker.

- # In the two-generation reproduction study, a comparison of the doses at which cholinesterase inhibition occurred in adults (0.2 mg/kg/day) versus pups (1.7 mg/kg/day) indicate that the pups may be less sensitive than adults to the cholinesterase-inhibiting effects of tribuphos.

Developmental Neurotoxicity

The Committee determined that a developmental neurotoxicity study is *required.* The concern for the developmental neurotoxic potential of tribuphos was elicited by neuropathological lesions in the subchronic study with hens (MRID 42007202) and in the combined chronic toxicity/carcinogenicity study in rats (MRID 42335101), as well as data gaps for acute and subchronic neurotoxicity studies in rats.

Data Gaps

Acute Neurotoxicity - Rat (§81-8)

Subchronic Neurotoxicity - Rat (§ 82-5)

Special Subchronic Neurotoxicity - Rat (non-guideline study)

Developmental Neurotoxicity - Rat (non-guideline study)

Magnitude Of The Residue In Plants (§171-4; d, k & j)

Conclusions

HIARC recommended that the **10 x** factor to account for enhanced sensitivity of infants and children (**as required by FQPA**) **should be retained. The OPP FQPA Safety Factor Committee will make a final determination as to the applicability of the FQPA factor**. Although no increased sensitivity of fetuses as compared to maternal animals were observed following *in utero* exposure in developmental toxicity studies and no increased sensitivity of pups as compared to adults were observed in a multigeneration reproduction study, the Committee determined that the 10x to account for enhanced sensitivity of infants and children is required because:

(i) Data gaps for acute and subchronic neurotoxicity studies;

(ii) Evidence of neuropathological lesions

(iii) There is concern for the developmental neurotoxic potential of tribuphos, based on the evidence of neuropathological lesions in the subchronic study with hens and in the combined chronic toxicity/carcinogenicity study in rats.

b. Reference Dose

The HED RfD Peer Review Committee recommended on January 3, 1997 that an RfD for this chemical be established on the chronic toxicity study (MRID 42007203) in the dog with a NOEL of 0.1 mg/kg/day (memo dated 7/14/97). In this study, the NOEL and LOEL for plasma cholinesterase inhibition were 4 and 16 ppm (0.1 and 0.4 mg/kg/day, respectively, in both males and females). The NOEL and LOEL for erythrocyte cholinesterase inhibition was 16 and 64 ppm (0.4 mg/kg/day in both males and females, and 1.7 and 2.0 mg/kg/day in males and females, respectively). The NOEL for brain cholinesterase inhibition was 64 ppm (1.7 mg/kg/day in males and 2.0 mg/kg/day in females), the highest dose level tested.

The Committee recommended that the chronic and reproductive toxicity studies in rats be used as co-critical studies along with the chronic toxicity study in dogs.

An Uncertainty Factor (UF) of 1000 was applied to account for both the interspecies extrapolation (10X), intraspecies variability (10X), and FQPA 10X factor based on positive neurotoxicity and neurotoxicity study data gaps. This uncertainty factor is based on a subsequent meeting of the HIARC which met on November 25th, 1997 (see details above under sensitivity to infants and children). **On this basis the RfD was calculated to be 0.0001 mg/kg/day.**

It should be noted that this chemical has not been reviewed by the WHO/FAO Joint Meeting of Pesticide Residues and an Acceptable Daily Intake (ADI) has not been established for this chemical.

c. Carcinogenicity Classification

Lifetime feeding studies in two species of laboratory animals are conducted to screen pesticides for cancer effects. When evidence of increased tumor incidence is noted in these studies, the Agency conducts a weight of the evidence review of all relevant toxicological data including short-term and mutagenicity studies and structure activity relationship.

The Cancer Peer Review Committee met on November 20, 1996 and January 8, 1997 to review the cancer classification of tribuphos (memo dated May 22, 1997). Using the revised Cancer Guidelines, the HED Cancer Peer Review committee concluded that the overall evidence in animals should be characterized as **"likely"** at high doses, based on increases in tumors in both sexes of CD-1 mouse and **"unlikely"** at low doses since all the tumor increases occurred only at the highest dose tested, 35.7 mg/kg/day (accompanied by severe toxicity). An acceptable chronic rat study was

conducted and no dose related increase in tumors were observed. A linear assessment based on tumors was not recommended, because of severe accompanying toxicity, typical of organophosphate chemicals, which occurred at all doses in the mouse. Therefore a non-linear approach (MOE) utilizing the most sensitive toxic endpoint was recommended. The most sensitive endpoint for chronic toxicity was plasma cholinesterase inhibition. A MOE approach should be used for quantification of human risk using the NOEL of 0.1 mg/kg/day, the lowest NOEL for cholinesterase inhibition, established in the 1-year dog study.

d. Developmental and Reproductive Toxicity Assessment

Tribuphos has been reviewed by the HED RfD Peer Review Committee (memo 7/14/97) which also determines if a review by the Developmental and Reproductive Peer Review Committee (DPRC) is required. The database for developmental toxicity and reproductive toxicity is considered be complete at this time. There was no indication of reproductive or developmental effects. The data demonstrated no indication of increased sensitivity of rats in utero and/or postnatal exposure tribuphos. This chemical was not referred to the DPRC and is not considered a developmental toxicant.

e. Other Toxicological Endpoints for Risk Assessment

The toxicological effects of a pesticide can vary with different exposure durations. HED considers the entire toxicity data base, and based on the effects seen for different durations and routes of exposure, determines which risk assessments should be done to assure that the public is adequately protected from any pesticide exposure scenario. Exposure scenarios can be dietary or non-dietary. Both short and long durations of exposure as well as routes of exposure are always considered. Typically, risk assessments include “acute”, “short-term”, “intermediate term”, and “chronic” risks. These assessments are defined as follows:

> Acute risk results from a one day or single event consumption of food and water, and reflects toxicity which could be expressed following oral exposure to the pesticide residues. High-end exposure to food and water residues are assumed.
>
> Short-term risk results from exposure to the pesticide for a period of 1-7 days, and therefore, overlaps with the acute risk assessment. This risk assessment was intended to address primarily dermal and inhalation exposure from pesticide applications. The assessment will be performed when there are primary dermal and inhalation exposures that result from residential or occupational exposures lasting from 1-7 days. However, the analysis for residential exposures will now address both dietary and non-dietary sources of exposure, and will typically

consider exposure from food, water, and residential uses when reliable data are available. In short term assessment, risks from average food and water exposure, and high-end residential exposure, are aggregated. High-end exposures from all three sources are not typically added because of the very low probability of this occurring in most cases, and because the other assumptions built into the assessment assure adequate protection of public health.

Intermediate-term risk results from exposure for 7 days to several months. This assessment is handled in a manner similar to the short-term risk assessment.

Chronic risk assessment describes risk which could result from several months to a lifetime of exposure. For this assessment, risks are aggregated considering average exposure from all sources for representative population subgroups including infants and children.

The TESC indicated that there are toxicological endpoints of concern for tribuphos as delineated in the TESC document dated 1/24/97 and the RfD/Hazard ID documents from 7/14/97 and 11/25/97. The conclusions are summarized below:

i. Acute dietary

The acute dietary endpoint is based on the teratology study (MRID 40190601) previously summarized. Dose and Endpoint for use in risk assessment is **NOEL of 1 mg/kg/day** based on decreases in plasma and RBC cholinesterase activity at 7 mg/kg/day (LOEL). A MOE of 1000 is considered appropriate to account for both the interspecies extrapolation (10X), intraspecies variability (10X), and FQPA 10X factor.

The Committee noted that ChE inhibition was seen on Day 16 and that ChE activity was not measured after the first day of dosing (i.e., after a single dose). This dose/endpoint was recommended because an assumption was made that ChE inhibition can occur after a single dose. This study is supported by the results observed in a teratology study with rabbits. In this study, when administered orally at doses of 0, 1, 3 or 9 mg/kg/day during gestation days 7 through 19, tribuphos caused significant decreases in plasma and RBC cholinesterase activity at all doses on day 20 and RBC at all doses on day 28. A NOEL was not established for ChE inhibition.

ii. Short-term (1-7 days) and Intermediate Term (1 week to several months) Dermal Exposure

For Short-and Intermediate Term dermal risk assessments, the **LOEL of 2 mg/kg/day** (the lowest dose tested) based on dose-dependent inhibitions of plasma, RBC and brain cholinesterase activity from a 21-day dermal toxicity study (MRID

42007201) in rabbits was selected as the endpoint to be used in short-term and intermediate term dermal risk assessments. This endpoint was supported by the LOEL of 2.6 mg/kg/day in the 90-day dermal toxicity study (MRID 42007202) in hens. A NOEL for whole blood cholinesterase was not established in the hen study as well.

TESC recommended the application of UFs account for inter-species (10x) and intra-species (10x) extrapolation. TESC also recommended an additional UF of 10x due the observance of severe neurotoxic effects seen in the hen study, thus indicating tribuphos is a potent neurotoxicant and for the use of a LOEL. HIARC concurred with TESC and determined that **a MOE of 1000 is required**. The additional UF of 10 is applied for FIFRA and not for FQPA. FQPA is not applicable for occupational exposure risk assessment. There are no registered residential uses of tribuphos.

iii. Chronic (Non-cancer) (Several Months Lifetime) Dermal Exposure

For **Chronic dermal risk assessment**, the TESC determined that based on the current use pattern (cotton), chronic exposure is not anticipated. However, if the use pattern changes,and a chronic dermal exposure scenario ensues as a result, then the TESC recommended that the **NOEL of 0.1 mg/kg/day** established in the chronic dog study should be used for this risk assessment.

iv. Inhalation Exposure (any time period)

For Short-, Intermediate- and Chronic-Term Inhalation risk assessments, the TESC recommended that the NOEL of 2.43 mg/L (0.9 mg/kg/day) established in the 90-day inhalation study (MRID 42399801) in rats should be used for this risk assessment. The TESC originally determined that based on the current use pattern and exposure scenario an inhalation risk assessment was not required. However, the available inhalation data indicate that the inhalation exposure is of concern for mixer/loaders and flaggers and an assessment is included. **A MOE of 100 is** adequate because 1) a NOEL was used for risk assessment and 2) FQPA is not applicable for occupational exposure risk assessment.

Table 3: Summary of Toxicological Endpoints for Tribuphos

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	ChE NOEL of 1 mg/kg/day (oral) based on decreases in plasma and RBC cholinesterase activity. Required MOE: 1000
Chronic (non-cancer)	Dietary	NOEL of 0.1 mg/kg/day based on inhibition of plasma cholinesterase activity. UF of 1000. RfD = 0.0001 mg/kg/day
Chronic (cancer)	Dietary/Dermal/ Inhalation	ChE NOEL of 0.1 mg/kg/day for a non-linear (MOE) approach - utilizing the most sensitive toxic endpoint for chronic toxicity - plasma cholinesterase inhibition.
Short-Term & Intermediate-Term	Dermal	ChE LOEL of 2 mg/kg/day (dermal) based on inhibitions of plasma, erythrocyte and brain cholinesterase activity. Required MOE: 1000
Chronic (noncancer)	Dermal	NOEL of 0.1 mg/kg/day based on inhibition of plasma cholinesterase activity. Required MOE: 1000
Inhalation (any time period)	Inhalation	NOEL of 2.43 mg/L (0.9 mg/kg/day) Required MOE: 100

3. Dietary Exposure and Risk Characterization

There is one technical product of tribuphos (98.0%) presently registered to Bayer Corporation (EPA Reg. No 3125-96). There are three end-use products, one registered to Bayer (EPA Reg. No 3125-282) and one each to Rhone-Poulenc Ag Company and Crystal Chemical Inter-America, EPA reg. Nos. 264-498 and 67801-3 respectively. There is also one Special Local Need (SLN) product registered in texas, (SLN #TX810045). The end-use and SLN formulations are 70.5%.

A comprehensive summary of the registered food/feed use patterns of tribuphos is presented in the Tolerance reassessment Summary (Table 4). The conclusions regarding the reregistration eligibilty of tribuphos on the commoditied listed in Table 4 are based on the use patterns registered by the basic producer, Bayer Corporation, taking into account the residues present on cotton-gin byproducts used as a feed item.

a. Dietary Exposure - Food Sources

i. Plant Metabolism

The reregistration requirements for plant metabolism are fulfilled. An acceptable study, depicting the qualitative nature of the residue in cotton plants, has been submitted and evaluated. The parent, tribuphos, was the principal residue identified, and accounted for >80% of TRR in/on cotton forage and 50% of TRR in/on cottonseed. Based on this study, the HED Metabolism Committee has determined that the residue of concern in/on plant commodities is tribuphos *per se*, which is the residue that is currently regulated. (40 CFR § 180.272)

ii. Animal Metabolism

The reregistration requirements for animal metabolism are fulfilled. Acceptable studies, depicting the qualitative nature of the residue in ruminant and poultry, have been submitted and evaluated. The HED Metabolism Committee (June 7, 1995) has concluded that the residue of concern in animal commodities is tribuphos *per se*, which is the residue that is currently regulated. The metabolism of tribuphos in ruminants and poultry is proposed to occur by hydrolysis of the parent butyl mercaptan, which is further metabolized and incorporated into natural products such as fatty acids, glycerides, and phospholipids. Butyl mercaptan may also be incorporated into proteins or converted 3-hydroxybutyl-methyl sulfone. 3-Hydroxybutylmethyl sulfone can form sulfate and glucuronic conjugates.

Based on the results of the poultry metabolism study, the Agency has concluded that a poultry feeding study is not required; there is no reasonable expectation of finite residues of tribuphos in eggs and poultry tissues [Category 3 of 40 CFR §180.6 (a)]. Because the ruminant metabolism study indicated a potential for residue accumulation and the residue of concern, tribuphos, was identified in milk and fat, a ruminant feeding study was required.

iii. Residue Analytical Method - Plants and Animals

The requirements for residue analytical methods are fulfilled for the purposes of reregistration. Acceptable methods are available for enforcement and data collection purposes for cottonseed commodities and milk. A method for the determination of tribuphos in animal tissues and milk that is a modification of PAM Vol. II, Method II has been submitted and is adequate for enforcement purposes.

iv. Storage Stability

Adequate storage stability data are available to support the storage intervals and conditions of samples of cottonseed, processed commodities of cottonseed (meal, hulls, and refined oil) and ruminant commodities used for tolerance reassessment. Storage stability data were submitted to support the confined rotational crop study. All

pertinent rotational crop samples used to characterize/identify tribuphos residues in rotational crops were stored for less than 30 days prior to analysis, negating the need for storage stability data. No additional storage stability data are required.

v. Magnitude of the Residue - Meat, Milk, Poultry & Eggs

There are no registered direct animal treatments for tribuphos on cattle, goats, hogs, horses, sheep, or poultry. Reregistration requirements for magnitude of the residue in meat, milk, poultry, and eggs are partially fulfilled and can be upgraded. An animal feeding study has been conducted on dairy cows fed tribuphos at 9 ppm, 33 ppm, and 121 ppm in their feed.

The HED Chemistry Exposure Assessment Committee (Chem SAC) met on March 18, 1998 to reconsider the use of cotton gin-byproducts containing tribuphos residues in the dairy and beef cattle diet. During the meeting a related issue was also discussed. Specifically, whether or not to use residue data on cotton leaves taken from a cotton metabolism study (S. Funk, 11/23/93; D169854 and D179581) in the absence of field trial data for cotton-gin byproducts to estimate tibuphos residues contributed to the animal diet from cotton-gin byproducts. The Chem SAC determined that 20% cotton gin-byproduct should be included in the animal diets, and that 200 ppm should be used as a default value for residues of tribuphos on cotton-gin by products based on the residue data on cotton leaves from the metabolism study. The 20% cotton-gin byproduct in the diet represents a maximum of this commodity in the animal diet (Table I OPPT 860 Guidelines), and 200 ppm represents an interpolated value of tibuphos residues on cotton leaves 7 days after application of tribuphos at 3X the seasonal maximum rate. The post-harvest interval (PHI) for this use of tribuphos on cotton is 7 days. Using the maximum percent of cotton-gin byproducts as recommended by the Chem SAC, and 200 ppm tribuphos residues in cotton leaves from the cotton metabolism study in lieu of field trial data on cotton gin byproducts, the animals theoretical dietary of tribuphos is 45 ppm. This is used as the 1x feeding level.

The existing tolerances for meat, meat byproducts (mbyp), and fat are all 0.02 ppm. The existing tolerance is adequate to cover residues of tribuphos expected from meat and mbyp. However, the existing tolerance for fat (0.02) appears to be too low. The existing tolerance for fat should be revoked and a tolerance of 0.15 ppm is recommended for tribuphos residues in fat. HED recognizes that the 1X dietary intake represents a conservative exposure assessment; however, because of the lack of data for cotton-gin byproducts, further refinements to dietary burden calculations cannot be made at this time.

Additional data concerning the tribuphos residues in milk from cows fed at the 6x feeding level should be submitted; alternatively, the registrants may petition to raise

the existing tolerance from 0.002 ppm to 0.01 ppm.

Tolerances for fat of cattle, goats, and sheep should be raised to 0.15 ppm.

Tolerances for residues of tribuphos in the fat, meat, and meat byproducts of hogs and horses at 0.02 ppm must be proposed.

Based on the results of the poultry metabolism study, the Agency has concluded that a poultry feeding study is not required; there is no reasonable expectation of finite residues of tribuphos in eggs and poultry tissues [Category 3 of 40 CFR §180.6 (a)].

vi. Magnitude of the Residue - Crop Field Trials/Processed Food/Feed

The reregistration requirements for magnitude of the residue in/on cottonseed and cotton gin byproducts are partially fulfilled. Field residue data are not available to support the registered spraying use patterns of tribuphos on cotton; see Attachment 1, Table A ("GLN 171-3: Directions for Use"). Unless the registrants wish to submit field residue data for these unsupported use patterns, these use patterns should be canceled or removed from all product labels.

Adequate field trial data, reflecting use of the registered EC formulation at the maximum registered use pattern, have been submitted for cottonseed. Field trial data submitted for cotton gin byproducts represent samples collected 14 days posttreatment; the established PHI is 7 days. HED recommends that six field trials be conducted reflecting the 7-day PHI, three trials for picker-harvested cotton and three trials for stripper-harvested cotton, with two samples of cotton gin byproducts collected from each trial. This additional data requirement should not impinge on the reregistration decision for tribuphos.

The reregistration requirements for magnitude of the residue in processed cottonseed commodities are fulfilled. An acceptable cottonseed processing study has been submitted; residues of tribuphos *per se* were not observed to concentrate in cottonseed meal, hulls, and refined oil.

Based on the submitted processing study, HED concluded that a tolerance for cottonseed hulls is not warranted. Therefore, the established feed additive tolerance of 6 ppm for cottonseed hulls should be revoked.

vii. Anticipated Residues

Anticipated residues consist of percent crop treated data and/or refined residue levels reflecting amounts more likely to occur than tolerance levels. Anticipated

residues for this chemical can ONLY be conducted with the percent crop treated data, i.e. 35% cotton crop treated (communication with BEAD 11/28/97 E.Brandt). In order to produce anticipated residues for meat and milk based on refined residue data, feeding studies conducted at the appropriate levels (e.g. 45 ppm, 135 ppm and 450 ppm) rather than the 9 ppm [not analyzed], 33 ppm, and 120 ppm levels of the submitted data are required (see section v. above for details). Additionally, ther are no cotton gin-by-products data conducted at less than a 14 day PHI and the label PHI is 7 days, which is potentially a significant difference relative to magnitude of the residues. Desiccants and/or late season herbicides used on cotton generally result in significant residues on cotton gin-by-products. For the purposes of risk assessment, it is appropriate to incorporate the percent crop treated data for anticipated residues, and assume the reassessed tolerances of 0.15 ppm for fat, and 0.01 ppm for milk in the absence of the appropriate data (see section v. above). These anticipated residues would not be considered overly conservative, especially the milk value, since: 1) tribuphos has been detected in milk at exaggerated feeding levels, 2) there is uncertainty of the residue levels consumed on cotton gin-by-products (which may be very high), and 3) we are unable to extrapolate from reasonable animal feeding study residue data.

viii. Tolerance Reassessment Summary / CODEX Harmonization

Tolerances Listed Under 40 CFR §180.272:

The tolerances listed in 40 CFR §180.272 are expressed in terms of tribuphos. The HED Metabolism Committee has concluded that tribuphos *per se* is the compound to be regulated. The tolerance expression is adequate.

Sufficient field trial data reflecting the maximum registered use patterns are available to ascertain the adequacy of the established tolerance for cottonseed; these data support the existing cottonseed tolerance.

Ruminant metabolism and feeding studies indicate that the established tolerances for the meat, and meat byproducts of cattle, goats, and sheep are adequate. Additional data concerning tribuphos residues in milk are required before the adequacy of the established tolerance for milk can be assessed. Based on the data currently available, milk and fat tolerances have been reassessed at 0.01and 0.15 ppm respectively. The term "negligible residues" should be removed from the tolerance expressions for fat, meat, and meat byproducts of cattle, goats, and sheep, and milk.

Tolerances Be Proposed Under 40 CFR §180.272:

Tolerances for residues of tribuphos in the meat, and meat byproducts of hogs

and horses at 0.02 ppm must be proposed. Once adequate data concerning tribuphos residues in cotton gin byproducts from cotton harvested at the established PHI are submitted, a tolerance for cotton gin byproducts must be proposed.

Tolerances Listed Under 40 CFR §186.5800:

Based on FQPA and the results of an acceptable cottonseed processing study, the established feed additive tolerance for cottonseed hulls should be revoked.

A summary of tribuphos tolerance reassessments is presented in Table 4 below.

Table 4. Tolerance Reassessment Summary for Tribuphos

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ *[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.272:			
Cattle, fat	0.02 [a]	0.15	
Cattle, meat	0.02 [a]	0.02	
Cattle, meat byproducts	0.02 [a]	0.02	
Cottonseed	4	4	*[Cotton, undelinted seed]*
Cotton Gin byproducts	none	TBD[b]	
Goats, fat	0.02 [a]	0.15	
Goats, meat	0.02 [a]	0.02	
Goats, meat byproducts	0.02 [a]	0.02	
Milk	0.002 [a]	0.01	
Sheep, fat	0.02 [a]	0.15	
Sheep, meat	0.02 [a]	0.02	
Sheep, meat byproducts	0.02 [a]	0.02	
Tolerances Be Proposed Under 40 CFR §180.272:			
Cotton, gin byproducts	None	TBD	New RAC according to Table I (OPPTS Series 860 Test Guidelines)
Hogs, fat	None	0.15	
Hogs, meat	None	0.02	
Hogs, meat byproducts	None	0.02	
Horses, fat	None	0.15	
Horses, meat	None	0.02	

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ *[Correct Commodity Definition]*
Horses, meat byproducts	None	0.02	
Tolerances Listed Under 40 CFR §186.5800:			
Cottonseed hulls	6	Revoke	Not warranted based on the results of an acceptable cottonseed processing study.

[a] Negligible residues.
[b] TBD = be determined.

CODEX HARMONIZATION

There are no Codex MRLs for tribuphos; therefore, no questions of compatibility with U.S. tolerances exist.

b. Dietary Exposure - Drinking Water

The available drinking water information is inadequate to fully assess exposure to tribuphos and its metabolites on a national level. However, information is available on local detections in California and Texas of tribuphos which can be used to extrapolate the following conclusions and generalizations.

i. Ground Water

A drinking water health advisory level for tribuphos has not been established; however, some groundwater data are available for tribuphos. According the EPA Pesticide in Groundwater Data Base: A compilation of Monitoring Studies, 1971 - 1991 A National Summary (EPA 734-12-92-001 Sept. '92) between 1984 and 1988, 569 wells were tested for tribuphos in the states of CA and TX, tribuphos was not detected in any of these samples. Although an absence of detections of tribuphos residues does not necessarily mean there is no exposure, environmental fate data indicates that tribuphos should not be a concern in ground water because it binds to the soil and appears to be immobile. Therefore, HED is not concerned about exposure to tribuphos residues in drinking water from ground water sources.

ii. Surface Water

Tribuphos can contaminate surface water at application by spray drift. Substantial

fractions of applied tribuphos may remain available for runoff for many months post-application (aerobic soil metabolism half-life of 745 days). The relatively high soil/water partitioning of tribuphos indicates that runoff will generally occur primarily via adsorption eroding soil as opposed to dissolution in runoff water.

Tribuphos is stable to abiotic hydrolysis at pHs 5 and 7, stable to direct aqueous photolysis, has a relatively low volatilization potential, undergoes slow abiotic hydrolysis at pH 9 and appears to undergo extremely slow biodegradation under aerobic conditions. Consequently, tribuphos will probably be persistent in the water column of most surface waters except those with short hydrologic residence times for which flow out of the system may be the major dissipation pathway. The results of the anaerobic soil metabolism study and the anaerobic aquatic metabolism study indicate that tribuphos may be a little less persistent under the anaerobic conditions found in most sediments, but that it will still be relatively persistent.

The Agency does not have any monitoring data from tribuphos in surface waters, but did perform refined (Tier 2) EECs for its use on cotton using the PRIZM2/EXAM II model. The refined EECs are for an edge of the field pond and represent upper bound estimates of concentrations that may occur in such systems. The EECs represent conservative screens for other types of surface waters, including flowing water and lakes and ponds not located at the edge of the field.

The estimated maximum concentrations of tribuphos in surface water is 14 ppb, and the estimated average concentrations of tribuphos in surface water is 5 ppb.

c. Dietary Risk Characterization

The dietary risk evaluation system (DRES) analyses were performed to estimate acute and chronic dietary risk for tribuphos. HED uses the DRES to combine the pesticide residue data with food consumption data. Thus, dietary (food source) exposure is equal to pesticide residues present in food multiplied by consumption data for the food item.

The consumption information used in this analysis is derived from USDA's 1977-78 Nationwide Food Consumption Survey (NFCS). Over 30,000 respondents were surveyed over three days as to what foods they ate, with each individual's consumption information being associated with their body weight, sex, age, ethnicity and other sociodemographic information. Individual consumption estimates were weighted to be nationally representative. From these data single day and 3 day average consumption estimates were derived for the U.S. population and select population subgroups. Three day average information is used in the DRES chronic exposure analyses.

HED acknowledges that the data from this survey are nearly dated. However, at this time, these data are the best information currently available to the Agency.

i. Chronic (Food), Non-Carcinogenic

Two chronic dietary exposure analyses (DRES) (from food sources) were conducted using the RfD of 0.0001 mg/kg/day (see Dose Response Section for details). One analysis used the reassessed tolerances for residues in/on cotton, milk, beef, goats, hogs, horses and sheep (see Table 4, Tolerance Reassessment Summary). The second analysis was conducted using the currently published tolerances from 40 CFR §180.272. Both analyses were conducted assuming 35% crop treated for cottonseed oil and cottonseed meal. No additional anticipated residue information was used in the analysis.

The anticipated residue contribution (ARC) from food was estimated for the general population and 22 population subgroups. The results for the general population and the most sensitive subpopulations are summarized below:

Table 5: Chronic Dietary Exposure and Risk from Food Sources

Population	ARC (mg/kg/day) published tolerances	%RfD [1] published tolerances	ARC (mg/kg/day) Reassessed tolerances	%RfD[1] Reassessed tolerances
U.S. population	0.000082	82%	0.000255	254%
Hispanics	0.000093	93%	0.000305	305%
Children (ages 1 6)	0.000171	171%	0.000586	585%
Children (ages 7 12)	0.000126	126%	0.000402	401%
Non-nursing infants <1 yr	0.000170	170%	0.000749	749%

[1] A percentage of the RfD that exceeds 100 is indicative of a risk concern.

The chronic dietary analysis (from food sources) has been partially refined, using percent-crop treated data. Tolerance level residues (whether published or reassessed due to reregistration) were used for meat and milk since data on livestock feeding studies conducted at appropriate levels and cotton gin-by-products is lacking. Cotton gin trash is considered a raw agricultural commodity and an animal feed commodity and can contribute up to 20% of the animal diet. By incorporating cotton gin trash residue data extrapolated from the metabolism study, in this risk assessment, the exposure to tribuphos in meat and milk may overestimated. For reassessed tolerances

recommended due to reregistration, the chronic dietary risk estimate is a concern since the percentage of the RfD exceeds 100 for all subpopulations.

ii. Carcinogenic Risk (food)

As discussed earlier, the HED Cancer Peer Review committee recommended a non-linear approach (MOE) utilizing the NOEL of 0.1 mg/kg/day based on plasma cholinesterase inhibition. The chronic dietary exposure figures in Table 5 were used to calculate MOEs for the U.S. Population.

Carcinogenic risk, for the U.S. population, was calculated using the following equation: MOE = NOEL / Exposure. For currently published tolerances the MOE is 1200 and for reassessed tolerances, the MOE is 390.

iii. Acute Dietary (Food) Risk

The acute dietary analysis (from food sources) estimates the distribution of single-day exposures for the overall U.S. population and certain population subgroups. The analysis evaluates individual 1 day food consumption as reported by the respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of tribuphos in the commodity supply.

Two acute dietary exposure analyses (from food sources) were conducted. One analysis used the reassessed tolerances for residues in/on cotton, milk, beef, goats, hogs, horses and sheep. The second analysis was conducted using the currently published tolerances from 40 CFR §180.272. Both analyses were conducted assuming 100% crop treated for all commodities and tolerance level residues on all commodities. No anticipated residue (ARs) information was used in the analysis.

The (MOE) is a measure of how close the exposure comes to the NOEL (the highest dose at which no effects were observed in the toxicity study selected), which is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). For this risk assessment acute dietary MOEs of 1000 or greater are considered not to be of concern.

Table 6: Acute Dietary (Food) Exposure and Risk Estimates

Table 6.a. Using Current Tolerancces

Population	TMRC (mg/kg/day)	MOE

	99th Percentile	High End Exposure[1]	99th Percentile	High End Exposure[1]
U.S. Population		0.001		1000
Infants (<1 year)		0.001		1000
Children (1-6 years)	0.001	0.0015	1000	660
Females (13+ years)		0.0005		2000
Males (13+years)		0.0005		2000

[1] For DRES, high end exposure represents ≥99.5th percentile..

Table 6.b. Using Reassessed tolerances.

Population	TMRC (mg/kg/day)		MOE	
	95th Percentile	High End Exposure[1]	95th Percentile	High End Exposure[1]
U.S. Population	0.0008	0.0016	1250	625
Infants (<1 year)	0.0016	0.003	625	333
Children (1-6 years)	0.0014	0.003	714	333
Females (13+ years)	0.0005	0.0008	2000	1250
Males (13+years)	0.0005	0.001	2000	1000

[1] For DRES, high end exposure represents ≥99.5th percentile.

[2] A MOE of less than 1000 is indicative of a risk estimate of concern.

For the reassessed tolerances, MOEs for infants less than one year old and children 1 - 6 years old exceed HED's level of concern even at the 95th percentile exposure level. This acute dietary risk estimate is conservative in that it assumes 100% crop treated and reassessed tolerance level residues on all commodities. The uncertainties noted in the Chronic Dietary Risk Section concerning appropriate tolerance levels for meat and milk are also present in this risk estimate.

iii. Aggregate Dietary Risk Estimate (Food and Drinking Water)

Tribuphos is a restricted use pesticide; therefore, tribuphos can be used only by certified applicators and cannot be purchased or used by the general public. HED has not identified any tribuphos products that are intended for home use, or uses in/around

schools, parks, or other public areas. Therefore, residential risk assessments are not appropriate.

FQPA requires that "aggregate exposure levels of consumers to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources" be considered. Since no residential uses have been identified for tribuphos, HED only anticipates aggregate exposure from dietary exposure - food and water sources.

No residues of tribuphos in ground water were detected in limited testing geared more toward herbicides rather than insecticides. Because there were no detections does not necessarily mean there is no exposure. However, environmental fate testing indicates that tribuphos should not be a concern in ground water because it binds to the soil and appears to be immobile. Therefore, exposure to tribuphos from ground water is not a concern at this time.

Acute Aggregate Risk Estimate

HED did not calculate drinking water levels of concern (DWLOC) for acute exposures to tribuphos in surface water for the general population, children and infants since the acute dietary risk estimate from food sources alone is at or exceeds HED's level of concern. HED did calculate the DWLOC for acute exposures for females (13+ years) and males (13+ years) relative to the acute toxicity endpoint. The acute dietary food exposure (from the DRES analysis) was subtracted from the ratio of the acute NOEL of 1.0 mg/kg/day (used for dietary assessments) and the MOE of 1000 to obtain the acceptable acute exposure for tribuphos in drinking water. DWLOCs were then calculated from this acceptable exposure using default body weights (60 kg for females & 70 kg for males) and drinking water consumption figures (2 liters). Based on this calculation HED's DWLOC for acute dietary risk is 15 ppb for females and 17.5 ppb for males.

For acute dietary risk estimated maximum concentrations of tribuphos are compared. In surface water concentrations of tribuphos are estimated from the PRIZM2/EXAM II model to be 14 ppb. The maximum estimated concentrations of tribuphos surface water are less than HED's levels of concern for acute exposure in drinking water. Therefore, HED concludes with reasonable certainty that residues of tribuphos in surface water used as drinking water do not contribute significantly to the aggregate acute human health risk estimate for females and males at the present time.

Short-term & Intermediate-term Aggregate Risk Estimate

Since there are no residential exposures expected with this proposed use, short and intermediate aggregate risk assessments will not be conducted.

Chronic Aggregate Risk Estimate

HED did not calculate drinking water levels of concern (DWLOC) for chronic exposures to tribuphos in surface water since the chronic dietary risk estimate from food sources alone is at or exceeds HED's level of concern for several subpopulations. Since the point of departure for both carcinogenic and chronic dietary risk is the same (NOEL of 0.1 mg/kg/day) based on plasma cholinesterase inhibition and tumor increases are only expected at high doses any mitigation measures for chronic (non-cancer) aggregate risk should adequately protect for cancer aggregate risk.

4. Occupational and Residential Exposure and Risk Characterization

a. Occupational and Residential Exposure

As stated earlier, HED has not identified any tribuphos products that are intended for home use, or uses in/around schools, parks, or other public areas. Therefore, residential assessments are not appropriate.

I. Use Patterns

Tribuphos is a defoliant used commercially for cotton crops. Tribuphos is specifically used to defoliate cotton in preparation for machine harvesting. Tribuphos accelerates the defoliation process by stimulating the formation of the abscission layer where the stem joins the stalk, causing the leaves and stems to drop cleanly to allow mechanical harvesting of the crop without staining the lint. Tribuphos is formulated as a liquid in emulsifiable concentrate (70 percent active ingredient), and as a liquid technical grade (97 percent active ingredient).

Tribuphos can be applied with aerial equipment and groundboom sprayers. Application rates vary from 1.5 - 1.875 pounds active ingredient per acre depending upon the application scenario. Tribuphos is applied only to cotton crops. Occupational exposure (short- and intermediate-term) is expected.

ii. Epidemiological Information

The OPP Incident Data System (IDS), Poison Control Centers database, California Department of Food and Agriculture database and the National Pesticide Telecommunications Network (NPTN) have been consulted for poisoning incident data on the tribuphos. From the review of the IDS and reports from California, it appears

that a significant number of spray drift cases result from the use of tribuphos. It is not clear from the information collected how many of these cases are due to anticholinergic effects versus the obnoxious odor of the pesticide. Some cases result in flu-like symptoms as a result of spraying tribuphos near residential areas. There were few too incidents involving mixer/loader workers that applied tribuphos for HED to make any conclusions.

iii. Handler Exposure and Risk Estimate

EPA has determined that there are potential exposures to mixers, loaders, applicators, and other handlers during usual use-patterns associated with tribuphos. Based on the use patterns, five major exposure scenarios were identified for tribuphos:

(1a) mixing/loading liquids for aerial application;
(1b) mixing/loading liquids for groundboom application;
(2) applying sprays with a fixed-wing aircraft;
(3) applying sprays with a helicopter;
(4) applying sprays with groundboom equipment; and,
(5) flagging for aerial spray applications.

Occupational exposure data are available reflecting short-term and intermediate-term dermal and inhalation exposures. **The available chemical-specific data are included in the Pesticide Handlers Exposure Database (PHED) Version 1.1.** Therefore, a separate assessment of the chemical-specific data are not necessary. Table 4 presents the estimated short- and intermediate-term dermal exposure to tribuphos using a combination of chemical-specific and surrogate data. Table 5 presents dermal risk estimates for tribuphos for both the short-term and intermediate-term exposures. Table 6 presents inhalation risk estimates for tribuphos for both the short-term and intermediate-term exposures. Table 7 summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

The registrant's chemical-specific handler exposure study (MRID No. 42685901) was designed to determine the dermal and inhalation exposures to the workers and to monitor their blood cholinesterase activity as per CDPR regulations. The study was conducted in California and Mississippi. The worker exposures in this study, and subsequent MOEs, were determined from dosimetry data. Although cholinesterase was also evaluated as a biological endpoint, **this was not a biomonitoring study per se.** Note that cholinesterase was monitored as required by the study protocol and California Environmental Protection Agency's Department of Pesticide Regulations (CDPR) guidelines. CDPR requires that workers be removed from pesticide handling in the event of significant cholinesterase depression. Group mean percentages of post-exposure baseline values for all job activities ranged from 95.8 - 106.9 for erythrocyte

cholinesterase and 95.9 - 107.5 for plasma cholinesterase.

Application rates included 1.127 lbs ai/acre at the maximum labeled rate of 1.877 lb ai/acre. Six groups of workers were evaluated: aerial crew mixer/loaders - closed system (8 replicates); ground crew mixer/loaders - closed system (8 replicates); aerial crew mixer/loaders - open system (8 replicates); aerial applicator/pilot (8 replicates); groundboom applicator (8 replicates); and aerial flaggers (16 replicates). In California, four commercial applicator crews were monitored (2 aerial and 2 ground crews). The mixer/loaders for the aerial applications used closed-system mixing equipment to mix Tribuphos from commercially available 500-gallon bulk containers with water in the mix tank and transfer the spray mixture to the aircraft. Ayers Corporation S2R-600 aircraft were used to apply Tribuphos. Flaggers assisted the pilots by directing their spraying patterns. Ground spray applications, also conducted in California, used closed-system mixing equipment. For the groundboom tractors, Tribuphos was open mixed in commercially available containers (30 gallon drums and 5 gallon cans) with water and then the diluted spray was transferred to the sprayer. The applicators used John-Deere Hi-Cycle boom sprayers equipped with air conditioned closed cabs to treat 531 acres of cotton. In Mississippi, the mixer/loaders mixed Tribuphos with water in open mix systems and then transferred the spray mixture to the aircraft. Aerial applications were not monitored in Mississippi. Applicator replicates ranged from 3.95 - 5.05 hours in the duration. The mixer/loader replicates ranged in duration from 1.55 - 4.8 hours.

The test subjects wore a long-sleeved, white, cotton or cotton synthetic blend tee-shirt and a pair of white cotton or cotton/synthetic blend tights (footless) as the whole body dosimeter. Cotton/polyester coveralls were worn over dosimeter garments. The mixer/loaders wore chemical-resistant gloves, aerial and groundboom applicators wore chemical-resistant gloves when exiting the cockpit/tractor cab. Workers also wore a baseball-type hat (or a helmet in the case of the pilots). Gauze patches were attached the outside of the worker's clothing at the chest, back, cap or helmet, and both forearms. Ethanol hand washes were used to monitor hand exposure. Personal air-sampling pumps and OVS-2 tubes were used to monitor potential inhalation exposure.

The quality assurance/quality control data (e.g., method validation, field recoveries, and storage stability) were collected and found be in the acceptable range. However, concurrent laboratory recovery data were not generated.

The following assumptions are made:

- Average body weight of an adult handler is 70 kg;
- Area treated in each scenario: a range of 350 to 1,200 acres for aerial applications (including flaggers and mixer/loaders supporting aerial applications), and 80 acres for groundboom applications; and

- Dust/mist respirator assumes a 5-fold protection factor.

Potential daily dermal exposure is calculated using the following formula:

Daily dermal exposure (mg ai/day) =
Unit exposure (mg ai/lb ai) x Use Rate (lb ai/A) x Daily Acres Treated (A/day).

No dermal absorption adjustment is necessary, since the toxicity endpoint is based on a study using the dermal route of exposure.

The daily dermal and inhalation dose is calculated using a 70 kg body weight for short-term exposure and a 70 kg body weight for intermediate-term exposure.

$$Daily\ Dose\left(\frac{mg\ ai}{Kg/Day}\right) = Daily\ Exposure\left(\frac{mg\ ai}{Day}\right) x \left(\frac{1}{Body\ Weight\ (Kg)}\right)$$

These calculations of daily dermal and inhalation doses of tribuphos received by handlers are used to assess the risk to those handlers. The short-term dermal MOEs were calculated using a dermal LOEL of 2 mg/kg/day and an inhalation NOEL of 0.9 mg/kg/day. The short-term and intermediate-term MOEs were calculated using the following formula:

$$MOE = \frac{NOEL\left(\frac{mg}{kg/day}\right)}{Daily\ Dose\left(\frac{mg}{kg/day}\right)}$$

Table 7: Short-term and Intermediate-term Dermal Exposures to Tribuphos

Exposure Scenario (Scen.#)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (μg/lb ai)[b]	Application Rate (lb ai/acre)[c]	Daily Acres Treated[d]	Daily Inhalation Exposure (mg/day)[e]	Daily Dermal Exposure (mg/day)[f]
Mixer/Loader Exposure						
Mixing/Loading Liquids for Aerial Application (1a)	2.9	1.2	1.875	(1) 350 (2) 1,200	(1) 0.79 (2) 2.7	(1) 1,903 (2) 6,525
Mixing/Loading Liquids for Groundboom Application (1b)			1.875	80	0.18	435.00
Applicator Exposure						
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	1.875	(1) 350 (2) 1,200	See Engineering Controls	See Engineering Controls
Applying Sprays with a Helicopter (3)	See Engineering Controls	See Engineering Controls	1.875	(1) 350 (2) 1,200	See Engineering Controls	See Engineering Controls
Applying Sprays with a Groundboom Sprayer (4)	0.014	0.74	1.875	80	0.11	2.10
Flagger Exposure						
Flagging Aerial Spray Applications (5)	0.011	0.35	1.875	(1) 350 (2) 1,200	(1) 0.23 (2) 0.79	(1) 7.2 (2) 25

[a] Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor. Baseline data are not available for aerial application.

[b] Baseline inhalation exposure represents no respirator.

[C] Application rates are maximum values found in the tribuphos labels.

[d] Daily acres treated values are from the EPA OREB estimates of acreage that could be treated in a single day for each exposure scenario of concern. A range of acres treated is reported for aerial applications to cotton.

[e] Daily Inhalation Dose (mg/day) = Inhalation Unit Exposure (μg/lb ai) * (1 mg/1,000 μg conversion) * Appl. rate (lb ai/acre) * Acres treated.

[f] Daily Dermal Dose (mg/day) = Dermal Unit Exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated.

Table 8: Short-term and Intermediate-term Dermal Risk Estimates for Tribuphos

Exposure Scenario (Scen #)	Baseline Dermal Dose (mg/kg/day)[a]	Baseline Dermal MOE[b]	Risk Mitigation Measures					
			Additional PPE			Engineering Controls		
			PPE Dermal Unit Exp. (mg/lb ai)[c]	PPE Daily Dermal Dose (mg/kg/day)[a]	PPE Dermal MOE[b]	Eng. Controls Dermal Unit Exposure (mg/lb ai)[d]	Eng. Controls Dermal Daily Dose (mg/kg/day)[a]	Eng. Controls Dermal MOE[b]
Mixer/Loader Risk Estimate								
Mixing/Loading Liquids for Aerial Application (1a)	(1) 27 (2) 93	(1) 0.07 (2) 0.02	0.017	(1) 0.16 (2) 0.55	(1) 13 (2) 3.6	0.0086 (gloves)	(1) 0.081 (2) 0.018	(1) 25 (2) 7
Mixing/Loading Liquids for Groundboom Application (1b)	6.2	0.3		0.036	56		0.018	110
Applicator Risk Estimate								
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	0.005	(1) 0.047 (2) 0.16	(1) 43 (2) 13
Applying Sprays with a Helicopter (3)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	0.0019	(1) 0.018 (2) 0.061	(1) 110 (2) 33
Applying Sprays with a Groundboom Sprayer (4)	0.03	67	0.011	0.024	83	0.005	0.011	180
Flagger Risk Estimate								
Flagging Aerial Spray Applications (5)	(1) 0.1 (2) 0.36	(1) 20 (2) 6	0.01	(1) 0.094 (2) 0.32	(1) 21 (2) 6.3	0.00022	(1) 0.0021 (2) 0.0071	(1) 950 (2) 280

[a] Dermal Dose (mg/kg/day) = Dermal Exposure (mg/day) / Body weight (70 kg). The baseline dermal exposure, application rates, and acres treated are listed in Table 4. A range of application rates are reported for aerial applications to cotton: (1) 350 acres, and (2) 1,200 acres.

[b] Dermal MOE = LOEL 2 (mg/kg/day) / Daily Dermal Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern.

[c] Additional PPE:
Scenario 1a, 1b, & 4: Double layer of clothing and chemical resistant gloves.
Scenario 5: Double layer of clothing and no gloves.

[d] Engineering Controls:
Scenario 1a and 1b: Closed mixing/loading, single layer of clothing, chemical resistant gloves.
Scenario 2, 3, & 4: Enclosed cockpit or cab, single layer of clothing, no gloves.
Scenario 5: Enclosed truck, single layer of clothing, no gloves

Table 9: Short-term and Intermediate-term Inhalation Risk Estimates to Tribuphos

Exposure Scenario (Scen #)	Baseline Inhalation Dose (mg/kg/day)[a]	Baseline Inhalation MOE[b]	Risk Mitigation Measures					
			Additional PPE -- Dust/Mist Respirator (5-Fold Protection Factor)			Engineering Controls		
			PPE Inhalation Unit Exp. (μg/lb ai)[c]	PPE Daily Inhalation Dose (mg/kg/day)[a]	PPE Inhalation MOE[b]	Eng. Controls Inhalation Unit Exposure (μg/lb ai)[d]	Eng. Controls Inhalation Daily Dose (mg/kg/day)[a]	Eng. Controls Inhalation MOE[b]
Mixer/Loader Risk Estimate								
Mixing/Loading Liquids for Aerial Application (1a)	(1) 0.011 (2) 0.039	(1) 82 (2) 23	0.24	(1) 0.0023 (2) 0.0077	(1) 390 (2) 120	NA	NA	NA
Mixing/Loading Liquids for Groundboom Application (1b)	0.0026	350		NA	NA		NA	NA
Applicator Risk Estimate								
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	0.068	(1) 0.00064 (2) 0.0022	(1) 1,400 (2) 410
Applying Sprays with a Helicopter (3)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	0.0018	(1) 0.000017 (2) 0.000058	(1) 53,000 (2) 16,000
Applying Sprays with a Groundboom Sprayer (4)	0.0016	560	NA	NA	NA	NA	NA	NA
Flagger Risk Estimate								
Flagging Aerial Spray Applications (5)	(1) 0.0033 (2) 0.011	(1) 270 (2) 82	0.07	(1) NA (2) 0.0023	(1) NA (2) 390	NA	NA	NA

NA - Not applicable, previous MOE greater than 100.

[a] Inhalation Dose (mg/kg/day) = Inhalation Exposure (mg/day) / Body weight (70 kg); the baseline inhalation exposure, application rates, and acres treated are listed in Table 4. A range of application rates are reported for aerial applications to cotton: (1) 350 acres, and (2) 1,200 acres.

[b] Inhalation MOE = NOEL 0.9 (mg/kg/day) / Daily Inhalation Dose (mg/kg/day). MOEs of greater than 100 do not indicate a risk estimate of concern.

[c] Additional PPE: Dust/Mist respirator (5-fold protection factor).

[d] Engineering Controls: Scenario 2 and 3 enclosed cockpit.

Table 10: Exposure Scenario Descriptions for the Use of Tribuphos

Exposure Scenario (Number)	Data Source	Standard Assumptions (8-hr work day)	Comments
Mixer/Loader Descriptors			
Mixing/Loading Liquid Formulations (1a and 1b)	PHED V1.1 and MRID No. 426859-01	range of 350 to 1,200 acres for aerial, 80 acres for groundboom.	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; Dermal = 72 to 122 replicates; and Inhalation 85 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. hands = 59 replicates and Dermal = 72 to 122 replicates. High confidence in dermal data. **Engineering Controls:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 31 replicates and Dermal = 16 to 22 replicates. High confidence in dermal data. PHED data used for baseline, no protection factors (PFs) were necessary. A 50 percent PF was used for PPE represent double layer of clothing. Gloves were worn during use of engineering controls.
Applicator Descriptors			
Applying Sprays with a Fixed-wing Aircraft (2)	PHED V1.1 and MRID No. 426859-01	range of 350 to 1,200 acres.	**Engineering Controls:** "Best Available" grades: Hands = acceptable grades, and dermal and inhalation ABC grades. Hands = 34 replicates; Dermal = 24 to 48 replicates; Inhalation = 23 replicates. Medium confidence in dermal and inhalation data. PHED data used no PFs were necessary.
Applying Sprays with a Helicopter (3)	PHED V1.1 and MRID No. 426859-01	range of 350 to 1,200 acres.	**Engineering Controls:** "Best Available" grades: Hands and dermal = A,B,C grades. Inhalation = acceptable grades. Hands = 2 replicates; Dermal = 3 replicates; and Inhalation = 3 replicates. Low confidence in dermal and inhalation data. PHED data used no PFs were necessary.

Exposure Scenario (Number)	Data Source	Standard Assumptions (8-hr work day)	Comments
Applying Sprays with a Groundboom Sprayer (4)	PHED V1.1 and MRID No. 426859-01	80 acres.	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 29 replicates; Dermal = 23 to 42 replicates; and Inhalation = 22 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grade: Dermal grades acceptable; hand grades A,B,C. Hands = 21 replicates; Dermal= 23 to 42 replicates. Medium confidence in dermal data. **Engineering Controls:** "Best Available" grade: Dermal of hands grades A,B,C. Hands= 16 replicates; Dermal= 20 to 31 replicates. Medium confidence in dermal data. PHED data used for baseline and engineering controls, no PFs were necessary. A 50 percent PF was used for PPE represent double layer of clothing.

Exposure Scenario (Number)	Data Source	Standard Assumptions (8-hr work day)	Comments
Flagger Descriptors			
Flagging Aerial Spray Applications (5)	PHED V1.1 and MRID No. 426859-01	range of 350 to 1,200 acres.	**Baseline, PPE, and Engineering Controls:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 16 replicates; Dermal = 16 to 18 replicates; and Inhalation = 28 replicates. High confidence in dermal and inhalation data. PHED data were used for baseline, no PFs were necessary. A 50 percent PF was added for PPE represent coveralls. A 98% PF was added for Engineering Controls represent flagging from an enclosed truck.

[a] Standard Assumptions based on an 8-hour work day as estimated by HED. BEAD data were not available.

[b] "Best Available" grades are defined by HED SOP for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates

iv. Post Application Exposure and Risk Estimates

A chemical specific study was conducted to determine the dermal and inhalation exposures (and to monitor the blood cholinesterase activity, as per CDPR regulations) of 10 replicates for *picker operators*, 6 replicates for *module builder operators*, 10 replicates for *rakers*, and 4 replicates for *trampers* as they conducted their activities in tribuphos treated cotton fields (MRID No. 42701601). In addition, this study was used to compare dermal exposure and dislodgeable residue data to calculate a dermal transfer coefficient for each job category. The worker exposures in this study, and subsequent MOEs, were determined from dosimetry data. Although cholinesterase was also evaluated as a biological endpoint, this was not a biomonitoring study per se. Review of the individual and group mean cholinesterase monitoring results for workers in each job category indicates that all post-exposure cholinesterase values were within acceptable limits. None of the workers had to be removed from exposure due to a significant cholinesterase depression (erythrocyte cholinesterase value, 70% of baseline) as required by the study protocol and CDPR regulations.

Tribuphos was applied to cotton fields at a maximum proposed label rate of 2.5 pints/acre (equal 1.9 lbs ai/acre). For the reentry exposure portion of the study, 2 sites in the San Joaquin Valley, CA were used. For the dislodgeable residue portion of the study, 2 residue trials were conducted in Mississippi and 2 were conducted in California. Tribuphos was applied using either aerial equipment or power-operated groundboom spray equipment.

In the reentry portion of the exposure study conducted in California, workers were monitored for dermal and inhalation exposure, as well as for blood cholinesterase activity after 15 and 17 days after treatment (DAT) from the aerially treated field, and 20 DAT from the ground-treated field. Dermal exposures were monitored using gauze patch dosimeters on different parts of the worker's body, whole body dosimetry, and solvent hand rinses. Inhalation exposures were monitored using personal air sampling within the breathing zone. The pumps were attached an OVSD-2 tube with a glass fiber filter with XAD-2 resin. The erythrocyte and plasma cholinesterase activity of workers was also monitored on a weekly basis for a 5-6 week period. The passive dosimetry results of these studies were used develop transfer coefficients for *picker operators*, *module builder operators*, *rakers*, and *trampers*.

Dislodgeable residues were measured by collecting cotton bolls (tribuphos is a defoliant). Cotton boll samples were collected 0, 1, 2, 4, 7 through 13, 15, and 17 DAT in California for the aerially treated field. For the field in California sprayed by ground equipment, samples were taken on 0, 1, 2, 4, 7 through 13, 15, 16, 17, 18 and 20 DAT. In Mississippi, samples were taken on 0, 1, 2, 4, 7 through 17 DAT for trial 1. For trial 2

in Mississippi, samples were taken prior to initial application and on 0,1,2,4, and 7 through 14 DAT. For the dislodgeable residue sample collection, each treated plot was divided into 3 subplots. At each sampling interval, one sample was collected from each subplot totaling 3 sample/interval/site. Cotton bolls were randomly selected, alternating from upper, middle, and lower parts of the plant to obtain a 50 g sample. The cotton bolls were then immersed in 200 ml of Nekal/water solution, shaken, squeezed and decanted in a sample container.

Field, laboratory, and storage stability data were generated for each matrix. Average recoveries were found to be in acceptable ranges.

The calculated dermal exposures, doses, and MOEs for the *picker operators*, *module builders*, *rakers*, and *trampers* are presented in Tables 8, 9, 10, and 11, respectively.

The transfer coefficients used for these tables were calculated using predicted dislodgeable residue data. The following transfer coefficients were used for each category: *picker operator* 92.36 ug/50g, *module builder operator* 26.13 ug/50g, *rakers* 150.98 ug/50g, and *trampers* 212.76 ug/50g. All of the transfer coefficients represent the arithmetic means of both the aerial and ground applications. For the *tramper*, data were only provided for the aerial exposure.

Potential average daily exposure (ADE) is calculated as follows:

$$\text{Potential ADE} = \frac{\text{DFR (ug/50g)} \times \text{Transfer Coefficient (50g/hr)} \times \text{Work Day (8 hr)}}{\text{Unit Adjustment from ug mg (1000ug)}}$$

Postapplication MOEs are calculated using the following formula:

MOE = LOEL (mg/kg/day)/Dose (mg/kg/day)

For tribuphos, the short- and intermediate-term LOEL for dermal toxicity is 2 mg/kg/day. A dermal absorption adjustment was not included since the toxicity endpoint is from a study using the dermal route of exposure. MOEs of greater than 1,000 do not indicate a dermal risk estimate of concern.

The postapplication inhalation exposure data collected on days 15, 17, or 20 after treatment do not indicate a risk estimate concern. The highest individual sample collected (day 15) was 14 μg/hr. Assuming an 8-hour work day and a body weight of 70 kg, the inhalation dose at 15 DAT would be 0.0016 mg/kg/day corresponding to a MOE

of 560. An inhalation MOE greater than 100 does not indicate an inhalation risk estimate of concern. The risks prior to day 15 were not estimated.

Table 11: Picker Operator Reentry Exposure Tribuphos Residues Application Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residue (μg/50g)[a]	Tc (50g/hr)[b]	Exposure (mg/day)[c]	Dose (mg/kg/day)[d]	MOE[e]
0	75.55	92.36	55.82	0.80	3
5	21.00	92.36	15.52	0.22	9
10	6.32	92.36	4.67	0.067	30
15	2.02	92.36	1.49	0.021	95
20	0.67	92.36	0.50	0.0071	282
25	0.23	92.36	0.17	0.0024	833
26	0.19	92.36	0.14	0.0020	1,000

[a] The average dislodgeable residues (i.e., cotton boll) from study MRID No. 427016-01, were derived by converting the measured dislodgeable residue data (μg/50 gram sample) into the natural log and then running a linear regression equation estimate the dissipation over time.

[b] Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residue (ug/50g cotton).

[c] Exposure (mg/day) = [(Best Fit Dislodgeable Residue (μg/50g) x Transfer Coefficient (50g/hr) / 1,000 μg/mg] x 8 hrs/day

[d] Dose (mg/kg/day) = Exposure (mg/day) / 70 kg.

[e] MOE = LOEL (2 mg/kg/day) / Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern.

Table 12: Module Builder Operator Reentry Exposure Tribuphos Residues Following Application Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residue (μg/50g)[a]	Tc (50g/hr)[b]	Exposure (mg/day)[c]	Dose (mg/kg/day)[d]	MOE[e]
0	75.55	26.13	15.79	0.23	9
5	21.00	26.13	4.39	0.063	32
10	6.32	26.13	1.32	0.019	105
15	2.02	26.13	0.42	0.0060	333
20	0.67	26.13	0.14	0.0020	1,000

[a] The average dislodgeable residues (i.e., cotton boll) from study MRID No. 427016-01, were derived by converting the measured DFR data (μg/50 gram sample) into the natural log and then running a linear regression equation estimate the dissipation over time.

[b] Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residue (ug/50g cotton).

[c] Exposure (mg/day) = [(Best Fit Dislodgeable Residue (μg/50g) x Transfer Coefficient (50g/hr) / 1,000 μg/mg] x 8 hrs/day

[d] Dose (mg/kg/day) = Exposure (mg/day) / 70 kg.

[e] MOE = LOEL (2 mg/kg/day) / Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern.

Table 13: Raker Reentry Exposure Tribuphos Residues Following Application Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residue (μg/50g)[a]	Tc (50g/hr)[b]	Exposure (mg/day)[c]	Dose (mg/kg/day)[d]	MOE[e]
0	75.55	150.98	91.25	1.30	2
5	21.00	150.98	25.36	0.36	6
10	6.32	150.98	7.64	0.11	18
15	2.02	150.98	2.44	0.035	57
20	0.67	150.98	0.81	0.012	167
25	0.23	150.98	0.12	0.0040	500
26	0.19	150.98	0.23	0.0033	606
27	0.15	150.98	0.18	0.0026	769
28	0.12	150.98	0.14	0.0020	1,000

[a] The average dislodgeable residues (i.e., cotton boll) from study MRID No. 427016-01, were derived by converting the measured dislodgeable residue data (μg/50 gram sample) into the natural log and then running a linear regression equation estimate the dissipation over time.

[b] Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residues (ug/50g cotton).

[c] Exposure (mg/day) = [(Best Fit Dislodgeable Residues (μg/50g) x Transfer Coefficient (50g/hr) / 1,000 μg/mg] x 8 hrs/day

[d] Dose (mg/kg/day) = Exposure (mg/day) / 70 kg.
[e] MOE = LOEL (2 mg/kg/day) / Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern.

Table 14: Tramper Reentry Exposure Tribuphos Residues Following Application Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residues (μg/50g)[a]	Tc (50g/hr)[b]	Exposure (mg/day)[c]	Dose (mg/kg/day)[d]	MOE[e]
0	75.55	212.76	128.51	1.84	1
5	21.00	212.76	35.74	0.51	4
10	6.32	212.76	10.76	0.15	13
15	2.02	212.76	3.44	0.049	41
20	0.67	212.76	1.14	0.016	125
25	0.23	212.76	0.39	0.0056	357
30	0.082	212.76	0.14	0.0020	1,000

[a] The average dislodgeable residues (i.e., cotton boll) from study MRID No. 427016-01, were derived by converting the measured dislodgeable residue data (μg/50 gram sample) into the natural log and then running a linear regression equation estimate the dissipation over time.

[b] Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residues (ug/50g cotton).

[c] Exposure (mg/day) = [(Best Fit Dislodgeable Residues (μg/50g) x Transfer Coefficient (50g/hr) / 1,000 μg/mg] x 8 hrs/day

[d] Dose (mg/kg/day) = Exposure (mg/day) / 70 kg.

[e] MOE = LOEL (2 mg/kg/day) / Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate concern.

b. Occupational Risk Summary and Characterization

Dermal and Inhalation Risk from Handler Exposures

Short-term and Intermediate-term

The calculations of short-term and intermediate-term dermal risk estimates indicate that the MOEs are more than 1,000 at baseline, additional PPE, or engineering controls for the following scenarios:

- None

The calculations of short-term and intermediate-term dermal risk estimates indicate that the **MOEs are not more than 1,000** despite the maximum mitigation measure for the following scenarios:

- (1a) mixing/loading liquids for aerial application;
- (1b) mixing/loading liquids for groundboom application;
- (2) applying sprays with a fixed-wing aircraft;
- (3) applying sprays with a helicopter;
- (4) applying sprays with a groundboom sprayer; and
- (5) flagging liquid aerial operations.

The calculations of short-term and intermediate-term inhalation risk estimates indicate that the MOEs are more than 100 at **engineering controls** for the following scenarios:

- (1a) mixing/loading liquids for aerial application at PPE;

(1b) mixing/loading liqiuds for groundboom application at baseline;

(2) applying sprays with a fixed-wing aircraft; and

- (3) applying sprays with a helicopter;

(4) applying sprays with a groundboom sprayer; and

(5) flagging liquiud aerial applications at baseline (350 acres treated) and at PPE (1,200 acres treated).

There are **data gaps** for the following scenarios, for which HED is unable to estimate risk:

- (2) baseline and PPE data for applying liquids with a fixed-wing aircraft.
- (3) baseline and PPE data for applying liquids with a helicopter aircraft.

NOTE: Only enclosed cockpit data are available.

HED recommends a meeting with SRRD to discuss handler risk estimate and risk mitigation options.

5. Required Studies

Chemistry Studies

Magnitude of the Residues - Crop Field Trials (§171-4; d, k, j)
(see Attachment 1)

Toxicology Studies

Acute Neurotoxicity - Rat (§81-8)

Subchronic Neurotoxicity - Rat (§ 82-5)

Special Subchronic Neurotoxicity - Rat (non-guideline study)

Occupational Handler Studies

Additional handler studies may be required pending the outcome of discussions on handler risk estimates and risk mitigation.

Occupational Post-Application Studies

Additional postapplication studies may be required pending the outcome of discussions on postapplication risk estimates and risk mitigation.

(RED SECTION IV - REGULATORY POSITION AND LABELING RATIONALE)

THIS SECTION IS DEFERRED PENDING A MEETING/DECISION WITH SRRD ON HANDLER AND POSTAPPLICATION RISK MITIGATION - PLEASE SEE DISCUSSION IN SECTION III OF THIS DOCUMENT.

(RED SECTION V - LABELING REQUIREMENTS)

THIS SECTION IS DEFERRED PENDING A MEETING/DECISION WITH SRRD ON HANDLER AND POSTAPPLICATION RISK MITIGATION - PLEASE SEE DISCUSSION IN SECTION III OF THIS DOCUMENT.

ATTACHMENT

Table A. Residue Chemistry Science Assessments for Reregistration of Tribuphos.

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References [1]
171-3: Directions for Use	N/A = Not Applicable	Yes [2]	
171-4 (a): Plant Metabolism	N/A	No	**42350009**
171-4 (b): Animal Metabolism	N/A	No	**42034502**, **42034503**, **42350010**, **42350011**
171-4 (c/d): Residue Analytical Methods			
- Plant commodities	N/A	No	42799001 [3], 42848001 [3], 42848002 [3], 42848003 [3]
- Animal commodities	N/A	Yes [4]	43837802 [5]
171-4 (e): Storage Stability	N/A	No[6]	42184701[7] , 42350009, 43821601[8] , 43837801 [5]
171-4 (k): Magnitude of the Residue in Plants			
- Cottonseed and gin byproducts	4 (seed) [§180.272]	Yes [2,9]	43837801 [5]
171-4 (l): Magnitude of the Residues in Processed Food/Feed			
- Cottonseed processed commodities	6 (hulls) [§186.5800]	No	43783701 [10]
171-4 (j): Magnitude of the Residue in Meat, Milk, Poultry, and Eggs			
- Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep	0.002 (milk); 0.02 (fat, meat, meat byproducts of cattle, goats, and sheep) [§180.272]	Yes [11]	43821601 [8]
- Eggs and the Fat, Meat, and Meat Byproducts of Poultry	N/A	No [12]	

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References [1]
171-4 (f): Nature and Magnitude of the Residue in Water	N/A	N/A	
171-4 (g): Nature and Magnitude of the Residue in Fish	N/A	N/A	
171-4 (h): Nature and Magnitude of the Residue in Irrigated Crops	N/A	N/A	
171-4 (i): Magnitude of the Residue in Food-Handling Establishments	N/A	N/A	
165-1: Rotational Crops (Confined)	--	No	42184701 [7]
165-2: Rotational Crops (Field)	--	No [13]	

1. **Bolded** references were evaluated in an Agency Memorandum, CBRS Nos. 8763 and 10031, DP Barcodes D169854 and D179581, 11/23/93, S. Funk; all other references were reviewed as noted.

2. No field residue data are available support LV/ULV application of tribuphos or aerial application of tribuphos using oil as a diluent. Unless the registrants wish submit field trial data support these applications, LV/ULV applications and aerial applications in which diesel oil may be used as a diluent should be deleted from product labels. The label should be amended clearly state the maximum seasonal use rate of 1.9 lbs. a.i./A.

   No field residue data are available support the registered SLN use of tribuphos. Unless the registrants wish submit data support use of tribuphos on cotton at 2.25 lb ai/A, this SLN should be canceled.

3. CBRS No. 12460, DP Barcode D194656, 12/8/95, C. Eiden.

4. The submitted method for the determination of tribuphos in animal tissues and milk is a modification of PAM Vol. II, Method II; independent laboratory and Agency validation is required before the method can be deemed adequate for use as an enforcement method.

5. CBRS No. 16554, DP Barcode D221143, 1/4/96, C. Eiden.

6. No further data on the storage stability data for tribuphos are required. CBRS No. 16989, DP Barcode D223962, 4/4/96, C. Eiden.

7. CBRS Nos. 14759 and 16457, DP Barcodes D209511 and D174442, 11/15/95, C. Eiden.

8. CBRS No. 16437, DP Barcode D220694, 12/18/95, C. Eiden.

9. CBRS recommends that six field trials be conducted reflecting the established 7-day PHI, three trials for picker-harvested cotton and three trials for stripper-harvested cotton, with two samples of cotton gin byproducts collected from each trial.

10. CRBS No. 16315, DP Barcode D219920, 11/14/95; C. Eiden

. Additional data concerning tribuphos residues in milk from cows fed at the 6x feeding level should be submitted; alternatively, the registrants may petition to raise the existing tolerance for milk from 0.002 ppm to 0.01 ppm.

. Tolerances for residues in the fat, meat and meat byproducts of hogs and horses at 0.02 ppm must be proposed.

. The requirement for a poultry feeding study was waived based on the results of the poultry metabolism study.

. No limited field rotational crop studies are required at this time and no plant back intervals are required for rotational crops.

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From:	S. Funk
To:	B. Sidwell/M. Wilhite
Dated:	11/23/93
MRID(s):	42034502, 42034503, 42350008-42350012

CBRS No.:	None
DP Barcode:	None
Subject:	Tribuphos. Issues to be Presented to the HED Metabolism Committee on 05/09/95.

Reregistration Case No. 2145. Chemical No. 74801.
From: C. Eiden
To: HED Metabolism Committee
Dated: 4/28/95
MRID(s): None

CBRS No.: None
DP Barcode: None
Subject: Tribuphos. Outcome of the 5/9/95 Meeting of the HED Metabolism Committee. Reregistration Case No. 2145. Chemical No. 74801.
From- C. Eiden
To: Files and HED Metabolism Committee
Dated: 6/7/95
MRID(s): None

CBRS No.: 16315
DP Barcode: D219920
Subject: Tribuphos. Reregistration List B. Chemical No. 074801. Case No. 2145. Cotton Processing Study. GLN: (171-4(l)).
From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 11/14/95
MRID(s): 43783701

CBRS No.: 14759 and 16457
DP Barcode: D209511 and D174442
Subject: Tribuphos. Reregistration List B. Chemical No. 074801. Case No. 2145. Rotational Crop Study. GLN: (165-1).
From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 11/15/95
MRID(s): 42184701

CBRS No.: 12460
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From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 12/18/95
MRID(s): 438216001

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To: Wilhite/B. Sidwell
Dated: 1/4/96
MRID(s): 43837801 and 43837802

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Subject: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Tribuphos.
From: B. Tarplee
To: Risk Characterization and Analysis Branch
Dated: 3/12/97
MRID(s): 426859-01 and 427016-01

DP Barcode: D234253
Subject: Review of DEF incident Reports, Chemical #074801
From: J. Blondell
To: B. Tarplee
Dated: 4/1/97